

Intrauterine effects of maternal weight dynamics



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Deze thesis draag ik op aan mijn gezin: het oude en het nieuwe.

Declaration

I hereby declare that except where specific reference is made to the work of others, the contents of this dissertation are original and have not been submitted in whole or in part for consideration for any other degree or qualification in this, or any other university. This dissertation is my own work and contains nothing which is the outcome of work done in collaboration with others, except as specified in the text and Acknowledgements. This dissertation contains fewer than 60,000 words excluding appendices, bibliography, footnotes, tables and equations.

Noor Else Willemien Dominique Teulings

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The details of my role and the role of other individuals in each chapter of this thesis are outlined below:

Chapter 1

I drafted the text. Dr Wood and Dr Sovio provided helpful comments.

Chapter 2

The study protocol was developed by Dr Katya Masconi and myself, with Dr Angela Wood advising on the protocol. I performed a review of the published literature using the following search engines: Pubmed, Ovid Embase, ClinicalTrial.gov and the Cochrane library. The literature search was duplicated by Dr Katya Masconi. Both Dr Katya Masconi and myself extracted the data and assessed the risk of bias in the selected publications. I wrote the R-code for the meta-analysis, performed the statistical analysis and prepared all tables & figures. I provided the first draft of the chapter, and Dr Katya Masconi and Dr Angela Wood provided helpful comments on the draft. I submitted the manuscript for publication and I was the corresponding author. This chapter has previously been published in BMC Pregnancy and Childbirth.

Chapter 3

Dr Ulla Sovio provided me with a cleaned data set of Pregnancy Outcome Prediction Study variables needed for this chapter. I drafted the text and Dr Wood provided helpful comments.

Chapter 4

The analysis plan was developed by Dr Catherine Aiken, Dr Angela Wood and myself. Dr Ulla Sovio provided me with a cleaned data set of Pregnancy Outcome Prediction Study variables needed for this chapter. I wrote the R-code for the analyses, performed the statistical analysis and produced all tables & figures. Dr Angela Wood provided statistical expertise on mixed linear regression models. Dr Angela Wood, Dr Ulla Sovio, Dr Catherine Aiken and Prof Gordon Smith provided helpful comments on the draft chapter and manuscript. I submitted this chapter as a manuscript for publication and I was the corresponding author. This chapter has previously been published in the International Journal of Obesity.

Chapter 5

I wrote the predefined analysis plan (see Appendix 2), Dr Angela Wood, Dr Ulla Sovio and Prof Gordon Smith provided detailed feedback. Dr Ulla Sovio provided me with a cleaned data set of Pregnancy Outcome Prediction Study variables needed for this chapter. I wrote the R-code for the analyses, performed the statistical analysis and produced all tables & figures. I wrote the draft chapter/manuscript. I submitted this chapter as a manuscript for publication and I am the corresponding author. Helpful feedback was provided by Dr Angela Wood, Dr Ulla Sovio and Prof Gordon Smith. This chapter has been submitted for publication.

Chapter 6

I wrote the predefined analysis plan (see Appendix 3), Dr Angela Wood, Dr Ulla Sovio and Prof Gordon Smith provided detailed feedback. Dr Ulla Sovio provided me with a cleaned data set of Pregnancy Outcome Prediction Study variables needed for this chapter. I wrote the R-code for the analyses, performed the statistical analysis and produced all tables & figures. I wrote the draft chapter/manuscript. Helpful feedback was provided by Dr Angela Wood, Dr Ulla Sovio and Prof Gordon Smith. This chapter is being prepared for publication.

Chapter 7

I drafted the text and Dr Angela Wood and Dr Ulla Sovio provided helpful comments.

Appendix A

I drafted the text and Dr Wood provided helpful comments.

Appendix B

This questionnaire is directly taken from the Pregnancy Outcome Prediction Study protocol that has been developed by Prof Gordon Smith, Dr Ulla Sovio and others.

Appendix C

This predefined analysis plan was developed by Dr Angela Wood, Dr Ulla Sovio, Prof Gordon Smith and myself.

Appendix D

This predefined analysis plan was developed by Dr Angela Wood, Dr Ulla Sovio, Prof Gordon Smith and myself.

Summary

Maternal obesity, and weight gain during or after pregnancy, are associated with adverse perinatal outcomes, as well as long-term cardiometabolic disease in the mother and offspring. Previous studies have demonstrated an association between maternal obesity and cardiovascular maladaptation to pregnancy. In turn, poor adaptation to pregnancy has been hypothesised to play an aetiological role in fetal growth restriction and the development of preeclampsia. This thesis aims to investigate the association between maternal weight dynamics and both cardiovascular adaptation to pregnancy and related perinatal outcomes.

First, a meta-analysis was conducted summarising the existing literature on the relationship between interpregnancy weight change and the risk of perinatal complications in a subsequent pregnancy. Interpregnancy weight gain was associated with a higher risk of gestational diabetes, preeclampsia, pregnancy induced hypertension and delivering a large-for-gestational age neonate. In contrast, interpregnancy weight loss was associated with a lower risk of delivering a large-for-gestational age neonate. Body mass index at the start of the first pregnancy modified this association; women with BMI $<25\text{kg/m}^2$ had a larger relative increase in risk than women with a BMI $\geq 25\text{kg/m}^2$.

To further assess the relationship between maternal weight dynamics and the risk of preeclampsia and fetal growth restriction, the Pregnancy Outcome Prediction Study dataset was utilised. This dataset comprised 4212 nulliparous women who attended the Rosie Hospital in Cambridge, UK. Women underwent serial research ultrasound scans at 20-, 28- and 36-weeks gestation, with the clinician and the patient blinded to the outcome. Additionally, pregnancy outcomes including birth weight and perinatal complications were recorded.

In the first study, maternal cardiovascular adaptation to pregnancy was assessed through the physiological drop in uterine and umbilical artery resistance throughout gestation. Obese women had a significantly smaller drop in uterine artery resistance between 20- and 36-weeks' gestation, compared to normal weight women (change -21.3% [95% confidence interval $-18.3, -24.3$] versus change -25.7% [$-24.3, -27.0$], respectively). In contrast, maternal obesity

did not affect the drop in physiological resistance in the feto-placental circulation.

The second study aimed to clarify the effect of the timing of gestational weight gain on the risk of perinatal complications. Weight gain during late gestation (28-36 weeks) was associated with a higher risk of developing preeclampsia, whereas weight gain during early gestation (12-28 weeks) was associated with a lower risk of delivering a small for gestational age neonate. Maternal prepregnancy BMI did not modify these associations.

While it is known that maternal obesity is associated with a lower risk of delivering a small for gestational age neonate, the final study tested the hypothesis that maternal obesity is associated with a higher risk of delivering a growth-restricted neonate as opposed to a constitutionally small neonate. Consistent with previous studies, maternal prepregnancy weight was associated with a lower risk of delivering a small for gestational age neonate. However, this association was irrespective of the presence of ultrasonic markers of fetal growth restriction.

In conclusion, maternal obesity is associated with impaired cardiovascular adaptation to pregnancy, although prepregnancy weight was not associated with reduced growth potential in the fetus. The timing of gestational weight gain was key, with late weight gain associated with higher preeclampsia risk and early weight gain with a lower risk of delivering a small for gestational age neonate.

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Nomenclature

Acronyms / Abbreviations

ACGV Abdominal circumference growth velocity

aOR Adjusted Odds Ratio

AUC Area Under the Curve

BMI Body Mass Index

BW Birthweight

CI Confidence Interval

cOR Crude Odds ratio

FGR Fetal Growth Restriction

GDM Gestational Diabetes

GWG Gestational Weight Gain

IQR Inter Quartile Range

LGA Large for Gestational Age

PE Preeclampsia

PIH Pregnancy Induced Hypertension

PI Pulsatility Index

POPS Pregnancy Outcome Prediction Study

PTB Preterm Birth

SD Standard Deviation

SGA Small for Gestational Age

UA-PI Umbilical artery pulsatility index

UtA-PI Uterine artery pulsatility index

wkGA Weeks gestational age

Chapter 1

Introduction

1.1 Chapter summary

The obesity rate has tripled worldwide since 1975 and is now thought to kill more people globally than undernutrition. In women of reproductive age, obesity in the UK has increased from 11% in 1993 to 21% in 2008, and in 2009 25% of UK women are thought to enter pregnancy obese. Maternal obesity is associated with various perinatal complications and a higher long-term risk of cardiovascular disease in the mother. Furthermore, maternal obesity can lead to a higher risk of childhood obesity and diabetes in the offspring via a phenomenon known as fetal programming, in addition to the known influence of environmental factors such as food availability and socioeconomic status on obesity prevalence.

Separate from the adverse effects of maternal obesity, gestational weight gain is also associated with perinatal complications. The Institute of Medicine in the US has issued guidelines for the recommended weight gain during gestation, based on a woman's prepregnancy BMI. It is estimated that >45% of all women gain weight above the Institute of Medicine recommendations. Exceeding the recommended weight gain is associated with adverse pregnancy outcomes but can also lead to increased postpartum weight retention and subsequently entering a following pregnancy with a higher BMI.

Two of the perinatal complications explored in this thesis are preeclampsia and fetal growth restriction, together known as the 'great obstetrical syndromes'. Obesity is one of the strongest risk factors for preeclampsia and there are many common background mechanisms that link obesity and preeclampsia, such as an increased state of inflammation, endothelial dysfunction and increased vascular resistance. The link between obesity and fetal growth restriction is less clear, as previous studies often have not distinguished between pathologically small neonates and constitutionally small neonates and it was therefore difficult to study true growth restriction. However, recent consensus on the definition (achieved by Delphi panel in 2015) aids research into this condition. It can be hypothesised that obesity leads to poorer placentation or cardiovascular adaptation to pregnancy and therefore a higher risk of the neonate not reaching its growth potential.

This chapter aims to identify literature gaps with regard to maternal weight dynamics and the risk of developing preeclampsia or delivering a growth restricted neonate. To do so, it will define and present the incidence and prevalence of maternal obesity, preeclampsia and fetal growth restriction. In addition, pathophysiology of the 'great obstetrical syndromes' will be described. Further, the long-term consequences of maternal obesity on maternal and

offspring cardiovascular health will be discussed. Finally, the aims and objectives of this thesis will be outlined.

1.2 Maternal weight dynamics in pregnancy

1.2.1 Maternal obesity

1.2.1.1 Definition

Obesity is defined as excessive fat accumulation and is often categorised by an individual's Body Mass Index (BMI), which is calculated by dividing a woman's weight (in kg) by her height squared (in meters). For adults, the World Health Organisation (WHO) has defined overweight as $\text{BMI} \geq 25 \text{ kg/m}^2$ and obesity as $\text{BMI} \geq 30 \text{ kg/m}^2$ [2]. This definition is similar for both sexes. A person's BMI should be considered a guide measurement, as it might not reflect the extent of fat accumulation for all individuals.

Women who enter pregnancy with a $\text{BMI} \geq 30 \text{ kg/m}^2$ are considered to have maternal obesity, although it can sometimes be difficult to exactly define prepregnancy obesity for research purposes. Routinely collected weight measurements at first midwife appointments or booking scans do not incorporate early gestational weight gain, which can therefore overestimate a woman's true prepregnancy BMI, albeit slightly. Another approach is to ask for self-reported weight and height, but this can systematically underestimate weight and overestimate height [3], leading to a lower-than-expected BMI measurement. However, associations with maternal and fetal outcomes do not seem to be systemically biased when self-reported BMI is used [4].

1.2.1.2 Epidemiology

Obesity has tripled worldwide since 1975 and is now estimated to cause more deaths globally than undernutrition [2]. In the United States, obesity amongst women of reproductive age (20-39 year) has risen from 8.9% between 1971-1974 [5] to 31.8% between 2011-2012 [6]. In Australia, incidence of both class II and class III obesity ($\text{BMI} > 35$ and $> 40 \text{ kg/m}^2$ respectively) increased significantly between 1998 and 2009 (from 1.2% to 2.0%, and 2.5% to 3.2%, respectively) [7]. Similarly, in England, the prevalence of obesity amongst women aged 25-34 was 11% in 1993, whereas this had risen to 21% in 2008. Based on WHO and Euro-Peristat data from 2009-2010, it is estimated that the United Kingdom has the highest prevalence of maternal obesity (25.5%) in Europe, whereas Poland reported the lowest (7.1%) [8] (Figure 1.1).

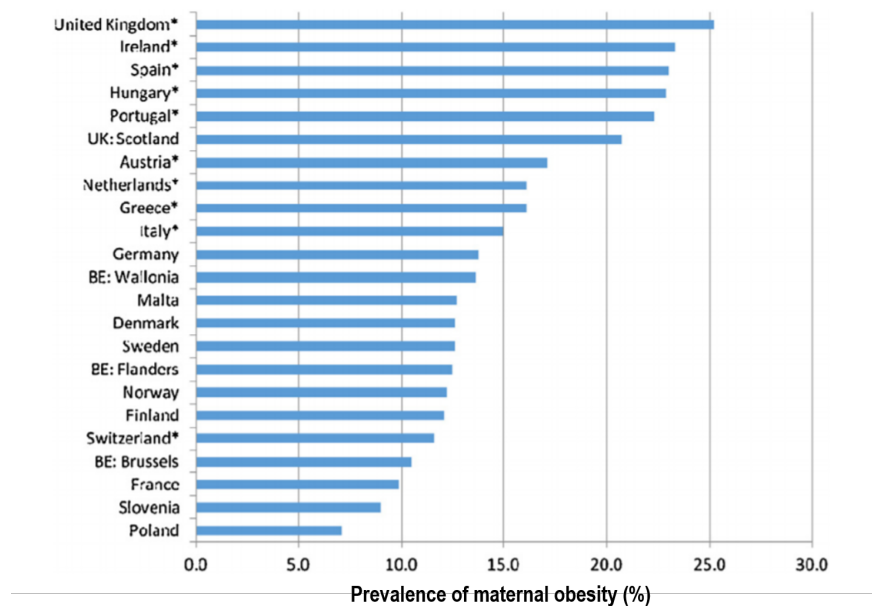


Fig. 1.1 Distribution of maternal obesity (Body Mass Index ≥ 30 kg/m²) from Euro-Peristat database and WHO. *From World Health Organisation database (2009) (globally higher rates due to general female population aged 20 or older). Adapted from Devlieger and colleagues [8].

There are marked differences of obesity rates depending on ethnicity and/or socioeconomic status. In the United States, obesity rates amongst white, non-Hispanic women aged 20-39 was estimated at 27.8%, whereas the rate amongst non-Hispanic black women was 55.8% and non-Hispanic Asian women 10.9% [6]. In the Dutch Generation R study, a prospective cohort study following women from early pregnancy, a monthly household income in the lowest category ($<€1600$) was associated with a 36% higher chance of being obese compared with an income of $>€2200$ /month [9]. Although not further stratified by age, the incidence of obesity amongst women within the highest quartile of the Index of Multiple Deprivation in England was 34% compared to 15% for women in the lowest deprivation quartile [10].

Additionally, obesity rates in lower- and middle-income countries (LMICs) have been following an upwards trend, particularly amongst poorer, rural communities. A shift from manual labour to more sedentary jobs could play a role in this shift [11]. Contrary to higher income countries, obesity seems to be more common in women than in men in most LMICs. Unfortunately, very few studies have explored the rate of obesity amongst pregnant women in LMICs. Using data from the Demographic Health Survey, maternal obesity rates in sub-Saharan Africa ranged from 5% in Ethiopia to 56% in Swaziland [12]. When investigating non-pregnant women of reproductive age, the prevalence of obesity in African countries

nearly doubled between 1991 and 2014, with the highest prevalence seen in Egypt (44.2% in 2014) and Madagascar reporting the lowest obesity prevalence (1% in 2014) [13].

1.2.1.3 Management of maternal obesity

Maternal obesity is associated with adverse perinatal outcomes, including an increased risk of gestational diabetes, hypertensive disorders of pregnancy, assisted deliveries and postpartum complications such as infection and haemorrhage [14]. The management of obese pregnant women is mainly focussed on screening and preventing these associated complications, and is aided in the UK by the National Institute for Health and Care Excellence (NICE) guidelines [15]. Ideally, care for these obese women would start pre-conception to achieve a healthy lifestyle before conceiving. Very few studies have addressed pre-conception interventions to prevent maternal obesity, and they are not conclusive on the effect of reducing perinatal complications [16]. Dieting in pregnancy is not recommended, as this might influence the health of the fetus, but a healthy diet and regular physical activity will benefit both mother and baby during pregnancy and help to achieve weight loss and maintain a healthy weight postpartum [15].

According to the NICE guidelines, all pregnant, including obese women, should be screened for hypertension and proteinuria at their first midwife appointment. Furthermore, the World Health Organisation and the American College of Obstetrics and Gynaecology recommend that all women with BMI $\geq 30\text{kg/m}^2$ should be screened for impaired glucose tolerance in early pregnancy [17], however NICE in the UK does not recommend structural screening in early pregnancy (17). Screening for hypertension and hyperglycemia, as markers of preeclampsia and gestational diabetes, respectively, could be warranted, as obesity is a risk factor for both conditions. Preeclampsia and its association with maternal obesity will be further discussed in **sections 1.3.1 and 1.4.1**.

1.2.2 Gestational weight gain

1.2.2.1 Definition

Gestational weight gain (GWG) can be defined as the amount of weight gained between conception and giving birth. Since 1990, the Institute of Medicine (IOM) in the United States has examined nutrition in pregnancy and published recommendations for optimal gestational weight gain to minimise adverse perinatal outcomes [18, 19]. The revised guidelines,

published in 2009, were updated to include four classifications of maternal prepregnancy BMI and to provide recommendations for total gestational weight gain, as well as a rate of weight gain throughout the second and third trimester [19]. The current weight gain recommendations according to the IOM can be found in Table 1.1.

Prepregnancy BMI (kg/m ²)	Total recommended GWG (kg) (range)	Rate of recommended GWG in second and third trimester (kg/week) (range)
Underweight (<18.5)	12.5-18	0.51 (0.44-0.58)
Normal weight (18.5-24.9)	11.5-16	0.42 (0.35-0.50)
Overweight (25-29.9)	7-11.5	0.28 (0.23-0.33)
Obese (≥ 30)	5-9	0.22 (0.17-0.27)

Table 1.1 Gestational weight gain recommendation, according to the Institute of Medicine (US) [19]

As there was a lack of evidence with regards to perinatal outcomes in obesity class II (≥ 35) or obesity class III (≥ 40) when the 2009 guidelines were developed, the guidelines recommend between 5 and 9kg GWG for women of all 'obese' classifications. It is shown that weight gain below the NAM recommendations, or even gestational weight loss, could have positive impact on outcomes in women from higher obesity classes [20, 21]. A recent study investigating the risks associated with GWG <5kg in different obesity classes showed that the odds for developing gestational hypertension, eclampsia or needing a Cesarean section were lower in all obesity classes compared to GWG between 5-9kg [22], confirming maternal health benefits in gestational weight loss and restricted weight gain [23, 24]. However, weight gain <5kg lead to substantially higher odds for neonatal outcomes such as preterm births and neonatal mortality [22]. Together, this evidence suggests that revisiting of the NAM guidelines to tailor recommendations for women of all obesity classes could improve perinatal outcomes.

1.2.2.2 Epidemiology

A large study by Deputy and colleagues reported the GWG in 30% of all pregnancies in the US between 2010 and 2011. They found that 20.9% of all women had inadequate GWG (lower than the IOM recommendations) and 47.2% reported excessive GWG (exceeding the IOM recommendations) [25], highlighting the need to be able to identify at risk women and inform much needed interventions.

As with prepregnancy BMI, the incidence of inadequate and excessive weight gain in pregnancy varies by ethnicity. In general, black and Hispanic women in the US are more likely to experience inadequate GWG and are less likely to have excessive GWG [26, 27]. Deputy and colleagues found the same pattern in normal weight women, but not in other BMI categories [25]. However, the IOM guidelines were developed based on a population with limited ethnic diversity, which could play a role.

In a normal pregnancy, the products of conception make up around 35% of the total GWG [28]. Total weight gain comprises approximately 8kg of water, 1kg of protein and between 1-6kg of adipose tissue [29]. Maternal BMI becomes a poorer prediction of excess adiposity during gestation, as the increased weight gained includes water and fetal components. However, data published in 2016 showed that excessive weight gain in pregnancy is associated with increased fat mass, but not with increased lean mass [30]. This correlation changes towards the end of pregnancy, as an increase in total body water contributes to a greater proportion of GWG [31].

1.2.2.3 Association between maternal obesity and gestational weight gain

Obese women, on average, gain less absolute weight during gestation than normal weight women, although more than 25% will gain more than 35 lbs (15.9kg) [32, 33]. In the study by Deputy et al., overweight and obese women reported the highest prevalence of excessive GWG relative to the recommendations set for them (64.1% and 63.5%, respectively), compared to 20.1% of underweight and 37.3% of normal weight women [25].

The IOM guidelines were updated in 2009 to include recommendations for obese women. Since they enter pregnancy with excess adipose tissue, the guidelines were aimed at obese women meeting recommended water and protein accrual but simultaneously avoiding additional adipose tissue accumulation. While some authors have suggested that weight gain below the IOM recommendations could improve some perinatal outcomes in obese women [34], inadequate weight gain can increase the risk of delivering a small for gestational age (SGA) neonate [21].

Little is known about the differences between normal weight and obese women regarding changes in body composition over the course of pregnancy. To further explore whether differences in composition between normal weight and obese women might be causative of perinatal complications, further research is warranted [35].

1.3 Maternal cardiovascular adaptation to pregnancy

1.3.1 Adaptation of the peripheral cardiovascular system

The maternal cardiovascular system undergoes major adaptive changes during pregnancy. As early as a few weeks after conception, there is a marked increase in cardiac output [36], resulting from an initial increase in heart rate followed by an increase in stroke volume (a result of increased plasma volume and higher venous return). The cardiac output plateaus towards the end of the second trimester [37], and peaks at a 30-50% increase in cardiac output compared to the prepregnancy state [38]. Simultaneously, the left ventricular end-systolic dimension (LVESD) decreases in the first trimester, most likely due to the increased heart rate and an increase in myocardial contractility [37]. In the second trimester, LVESD remains unchanged, but increases slightly towards term [39]. Consequently, the left ventricular mass increases during pregnancy [39], suggesting cardiac hypertrophy that sometimes compared to the response seen in physical training [37]. Collectively, this suggests an increased strain on the maternal heart during gestation.

During pregnancy, there is a fall in systemic peripheral vascular resistance, starting as early as 5 weeks gestation and continuing to fall up to 32 weeks. This drop in resistance is the result of flow and resistance changes in various peripheral vascular beds, such as the uterine and the renal circulations [40]. There is a disproportional large decrease in vascular resistance in the uterine circulation, which results in a larger proportion of the cardiac output being directed to the uteroplacental unit [41]. Towards the end of gestation, flow in the uterine artery circulation can reach up to 500ml/min. **Section 1.3.2** will explain more about the mechanism underlying the decrease in uterine resistance. Renal blood flow can reach up to 80% above prepregnancy levels, and this occurs simultaneously with a 50% increase in glomerular filtration rate [40].

In a non-complicated pregnancy, maternal systolic blood and diastolic blood pressure will drop in midgestation, to return to non-pregnant values towards term [37, 42]. From this it follows that the mean arterial pressure (MAP, calculated as $(\text{systolic blood pressure} + \text{diastolic blood pressure} \times 2)/3$) is lowest in the second trimester. Furthermore, this implies that systemic vascular resistance drops mid gestation as well, as it is the ratio of the cardiac output and MAP. As the cardiac output remains elevated till term, the systemic vascular resistance is also decreased until term [37].

1.3.2 Adaptation of the uteroplacental circulation

The haemodynamic adjustments in the maternal peripheral circulation promote an effective uteroplacental blood supply. One crucial part of the early adaptation of the uteroplacental circulation to pregnancy is the remodelling of the spiral arteries. Physiological spiral artery remodelling is thought to occur in five steps [43] (Figure 1.2): first, there is endothelial vacuolation and swelling of the vascular smooth muscle cells. Secondly, interstitial trophoblasts will invade the vascular smooth muscle cells, after which endovascular trophoblast cells appear and invade the lumen of the spiral arteries. The trophoblast will become embedded in the fibrinoid layer, which replaces the old vascular smooth muscle structure. Lastly, re-endothelialisation occurs. The remodelling of the spiral arteries is not only important to ensure adequate blood supply to the fetus to facilitate growth, but also to ensure that the fetal villi facilitating gas- and nutrient exchange are protected from high pressure and velocity circulation [1].

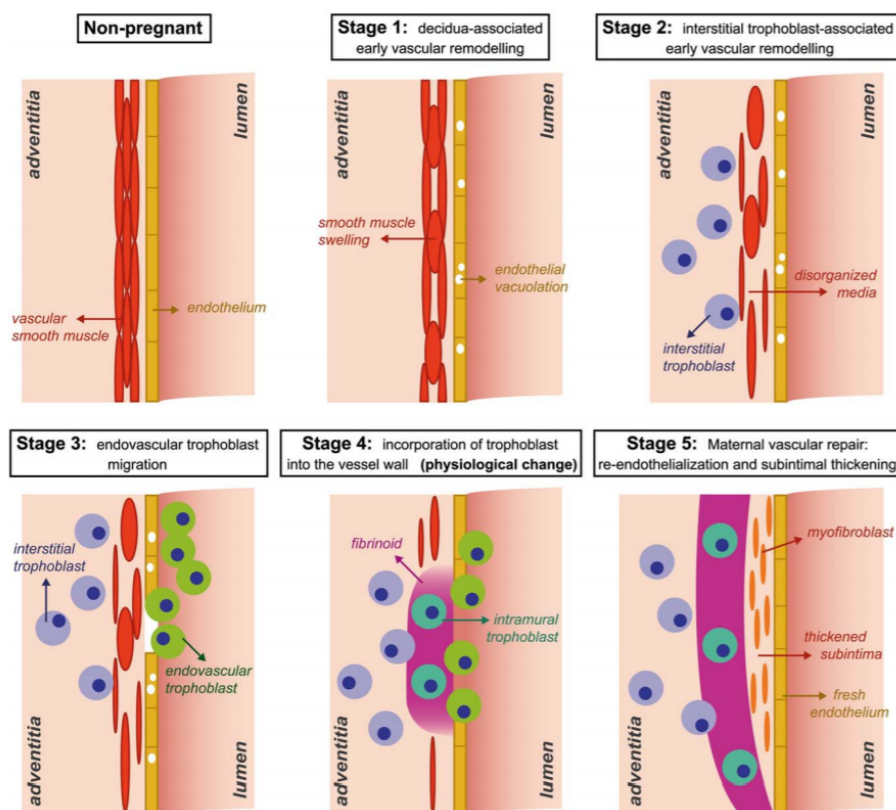


Fig. 1.2 Diagram showing the different steps in uterine spiral artery remodelling. Adapted from Pijnenborg and colleagues [43].

From the large mouths of the spiral artery, maternal blood will enter the intervillous space, which resembles a large lake of blood without impedance to blood flow. The placenta therefore acts as a large arterio-venous shunt. The maternal blood will pass over the surface of the placental villi and materno-fetal gas-, nutrient- and waste exchange takes place. The diameter of the end of the spiral arteries is crucial in lowering the speed with which the maternal blood enters the intervillous space, as incoming jets with a high velocity can create villous damage [44]. Burton and colleagues modeled that the spiral artery dilation rescued the velocity of the blood entering the intervillous space from 3 m/s to 10cm/s, depending on the exact radius and blood viscosity [1].

Although trophoblasts do not invade the radial arteries nor the uterine arteries, these vessels do undergo extensive dilation during pregnancy. The uterine artery doubles in diameter every 6.5 weeks of pregnancy [45]. The non-trophoblast induced dilation in the uterine artery is most likely the result of endocrine stimulation and flow-induced relaxation. Intraluminal flow and subsequent shear stress are a strong stimuli for vasodilation in pregnant women [46] and mediated by release of nitric oxide (NO) and prostacyclin. This relaxation is dependant on pregnancy status as no dilation is observed in non-pregnant women. One possible mechanism underlying the pregnancy-associated vascular relaxation to shear stress is an increase in 17β -Estradiol, which could either stimulates NO synthesis [47], and also possibly alters the sensitivity to shear stress [48]. Sex steroids seem to play a major role in the regulation of the uterine vascular tone in general, by mediating an up-regulation of the endothelial production of NO via increased eNOS expression and increasing eNOS activity [49].

A summary of the uterine and placental vasculature adaptation to pregnancy, showing (i) dilation of the uterine vasculature and (ii) spiral artery remodelling is shown in Figure 1.3

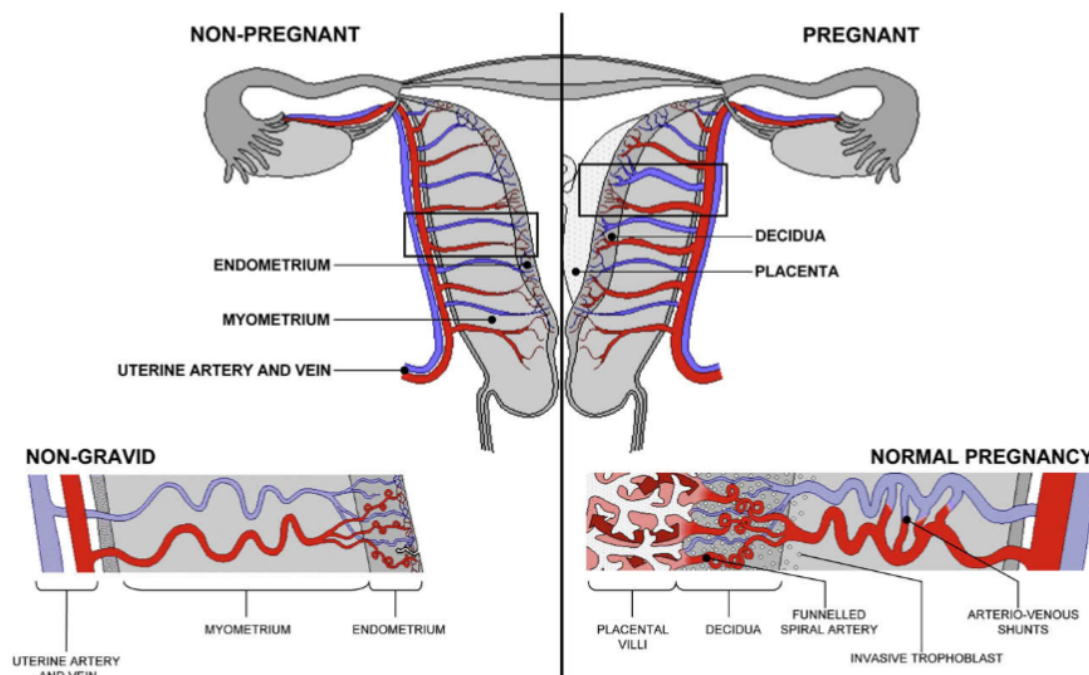


Fig. 1.3 Diagrammatic representation of uterine and placental vasculature (red shading = arterial; blue shading = venous) in the non-pregnant and pregnant state. Adapted from Burton et al. [1]

1.4 The ‘great obstetrical syndromes’

The term ‘great obstetrical syndromes’ was first proposed in 2009, in an editorial board meeting from the Journal of Maternal–Fetal and Neonatal Medicine. This term was created to refer to conditions that have multiple aetiologies, a long preclinical period, are adaptive in nature and have fetal involvement [50]. Furthermore, they are the result of complex interaction between maternal and fetal environment and genome [50]. The board suggests that aetiologic heterogeneity could be followed by a common pathway leading to the complications classified as ‘great obstetrical syndromes’. Therefore, the concept suggests that there is not one single test that will identify patients at risk of a great obstetrical syndrome, nor will there be a single treatment [50]. Both preeclampsia and SGA fetuses are categorised as great obstetrical syndromes, together with preterm labour, premature rupture of the membranes and stillbirth. The following sections will discuss the epidemiology, risk factors and pathophysiology of preeclampsia and delivering an SGA neonate in more detail.

1.4.1 Preeclampsia

1.4.1.1 Definition

Preeclampsia is one of the hypertensive disorders in pregnancy, and is defined according to the American College of Obstetrics and Gynaecology as (i) systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on two occasions, measured at least 4 hours apart after 20 weeks of gestation, in a woman with previously normal blood pressure and (ii) proteinuria ≥ 300 mg per 24-hour urine collection [51]. In the absence of proteinuria, preeclampsia can be defined as new onset hypertension (as described above) in combination with any of the following: (i) platelet count $< 100,000$ /microliter, (ii) serum creatinine concentrations > 1.1 mg/dL or doubling of the serum creatinine concentration with no history of renal disease, or (iii) elevated blood concentrations of liver transaminases to twice the normal concentrations [51].

Preeclampsia can be further subdivided by disease severity or by timing of presentation of the disease. Severe preeclampsia is defined preeclampsia with any of the following features: systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg, thrombocytopenia, impaired liver function (defined as twice the normal liver enzyme concentrations) progressive renal failure, pulmonary oedema or new-onset visual disturbances [51]. Early and late preeclampsia are defined by the timing of development of symptoms; < 34 weeks gestation is considered early, whereas ≥ 34 weeks gestation is classified as late [52–54]. It is hypothesised that early and late preeclampsia develop from different haemodynamics, which will be further discussed in **section 1.3.1.4** [52].

If preeclampsia is left untreated, it can further develop into eclampsia, and together they are one of the leading causes of maternal deaths worldwide, especially in low- and middle-income countries. The mortality rate from preeclampsia varies from 6.5/100,000 pregnancies in the United States [55], to 140/100,000 pregnancies in Nigeria [56] and 67/100,000 pregnancies in India [57]. Preeclampsia is also associated with fetal growth restriction and preterm birth, both spontaneous and iatrogenic.

Most women with preeclampsia are asymptomatic, therefore the disorder is often picked up through routine antenatal screening. In the UK, blood pressure measurements and urinalysis for proteinuria are carried out at each antenatal visit to screen for preeclampsia [58]. Furthermore, all pregnant women are advised to seek immediate advice from a healthcare professional if they experience any of the following symptoms of preeclampsia: severe

headache, problems with vision, severe epigastric pain, vomiting or sudden swelling of the face, hand or feet [58].

1.4.1.2 Epidemiology

Around 4% of first-time pregnancies are affected by preeclampsia, and around 2% of subsequent pregnancies [59], although the risk in multiparous women differs significantly depending on the history of preeclampsia in a previous pregnancy. For women without a history of preeclampsia in their first pregnancy, the risk in a further gestation was ~1%, while the risk was 15% for women with one previously affected pregnancy and 30% for two affected pregnancies, based on Swedish Medical Birth Register data between 1987-2004 [59]. The incidence of preeclampsia also increases with gestational age: ~0.4% of pregnancies were affected by early-onset and ~2.7% by late-onset preeclampsia in a population-based study according to a large hospital records study in Washington State (2003-2008) [54].

The prevalence of preeclampsia in the United States has risen from 2.5% in 1987 to 3.2% in 2004 [60], mainly due to an increase in the incidence of severe preeclampsia (Figure 1.4). Another national hospital database, including 120 million deliveries, estimated that the risk of developing severe preeclampsia was 6.7 fold higher for women delivering in 2003, compared to women delivering in 1980 [61]. It was hypothesised that a reduction in smoking rate and an increase in obesity has driven this trend, but also changes in the definition of preeclampsia might have contributed.

African American women are at higher risk of developing preeclampsia than Caucasian women, even when corrected for other known risk factors [62, 63]. Between 1979 and 2006 the rate of preeclampsia increased more for African American women than for Caucasian women, which Breathett and colleagues speculate could be explained by differences in obesity prevalence [64]. The association between obesity and preeclampsia will be further discussed in **section 1.4.1.1**.

1.4.1.3 Risk factors

Despite the high prevalence of preeclampsia, much of the aetiology of preeclampsia remains unknown. However, over the last decades multiple clinical and biochemical characteristics have been identified as risk factors. A summary of clinical risk factors and biochemical markers can be found in Table 1.2.

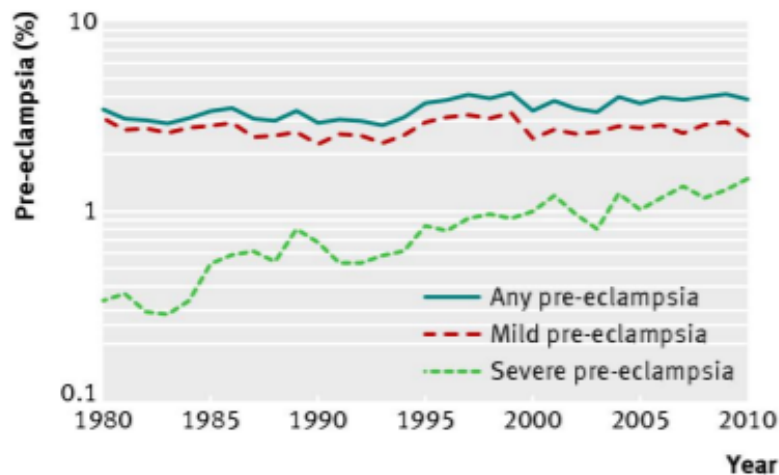


Fig. 1.4 Temporal changes in prevalence of pre-eclampsia (United States, 1980 to 2010). Adapted from Ananth et al. [61].

Clinical characteristics

One of the strongest pregnancy-related risk factors is nulliparity [63], with estimations that 75% of all preeclampsia cases are in nulliparous women [65]. Nulliparity almost triples the risk of preeclampsia compared to multiparity [66]. One of the popular hypotheses on the aetiology of preeclampsia is that of immune maladaptation, as the feto-placental unit is partially foreign due to paternal genes. Further supporting this hypothesis is the higher risk of preeclampsia after oocyte donation, change in partner and the protective effect of exposure to the sperm before conception [67].

Maternal systolic blood pressure and therefore also chronic prepregnancy hypertension are associated with a higher risk for preeclampsia too, and in one study was identified as the most predictive clinical feature [62]. This is classified as superimposed preeclampsia, and is particularly common in women with pre-existing cardiovascular or renal disease [68].

Studies investigating the effect of BMI on the risk of preeclampsia are difficult to pool, as many of them use different cut off values of BMI and different definitions of preeclampsia, but they all showed effects in the same direction [66]. When women with a ‘raised’ BMI at their first prenatal appointment are compared to normal weight women, the risk is increased by 50% [66], and a BMI $>35 \text{ kg/m}^2$ doubles the risk of developing preeclampsia [66]. Obesity is often associated with chronic hypertension, but even when patients with chronic hypertension are excluded, obesity is still associated with a higher risk [69].

Maternal characteristics	Clinical risk factors		Biochemical markers	
	Pregnancy characteristics	Maternal chronic disease	(Anti)angiogenic factors	Placental factors
Age <20 or >40 years	Nulliparous pregnancy	Chronic hypertension	Soluble fms-like tyrosine kinase 1	Pregnancy-associated plasma protein A
Black race	Interpregnancy interval >10 years	Diabetes mellitus (type 1 and type 2)	Placental growth factor	Placental protein 13 (PP13)
BMI >30 kg/m ²	Multiple gestation	Chronic renal disease	Vascular endothelial growth factor	Placental polyamines
Systolic blood pressure prepregnancy	Male fetus	Antiphospholipid syndrome		
Smoking status*	Conceived with assisted reproduction techniques	Systemic Lupus Erythematosus		
Previous preeclampsia, FGR or placental abruption	Change in partner from previous pregnancy			

Table 1.2 Clinical and biochemical risk factors for the development of preeclampsia [70, 71, 66, 44]. *negatively associated with the risk of developing preeclampsia.

Surprisingly, smoking is known to be associated with a decrease in the risk of preeclampsia, with a systematic review reporting a relative risk of 0.68 [95% confidence interval (CI) 0.67-0.69] for women smoking during pregnancy [72]. The protective effect also seemed dose related, and similar for nulliparous and multiparous or singleton and multiple fetuses gestation [73]. However, confounding of this relationship through a lower BMI in (heavy) smokers can not be excluded.

As early and late preeclampsia are often seen as two different subtypes of the disease, Valen-sise et al. investigated subtype specific risk factors [52]. They found that late preeclampsia was associated with a higher maternal BMI and higher maternal age, whereas early preeclampsia was more often associated with a normal BMI and abnormalities in haemodynamics in the uterine artery [52]. A large population-based cohort study confirmed these findings: younger maternal age was associated with early onset preeclampsia, whereas nulliparity was more strongly associated with late onset disease [54].

Biochemical risk factors

Pregnancy-associated plasma protein A (PAPP-A) is most commonly known for its use in combination with β -human chorionic gonadotropin and nuchal translucency thickness, to screen for Down's, Edwards and Patau syndrome in the first trimester [74]. However, decreased PAPP-A first trimester levels have also been associated with preeclampsia and preterm birth. When PAPP-A is used as a screening tool for preeclampsia alone, the positive predictive value is only 10-20% [75, 76], however when combined with Doppler ultrasound predictive value can go up to 70% .

The anti-angiogenic factor soluble fms-like tyrosine kinase 1 (sFlt-1) is increased in the placenta and serum of preeclamptic women [77]. sFlt-1 blocks placental growth factor (PlGF) from binding to the receptor, thereby introducing endothelial dysfunction. The elevated levels of sFlt-1 occur before the onset of symptoms and correlate with the time of onset of the disease [77]. As the levels of the proangiogenic PlGF are decreased in women at risk for preeclampsia, an easy way to improve prediction is to generate a ratio between sFlt-1 and PlGF. A meta-analysis of 20 studies showed that the sensitivity and specificity for this ratio was 0.78 and 0.84 respectively [78], with even higher Area Under the Curve (AUC) of 0.98 for the prediction of early-onset preeclampsia.

Recently, a novel predictor of preeclampsia was found in an untargeted maternal serum metabolomics analysis; 4-Hydroxyglutamate. This metabolite was strongly associated with early preeclampsia, independently of maternal characteristics [79], almost doubling the risk of preeclampsia with every standard deviation increase in the serum levels.

Mitigating risk

Women in the UK identified to be either at high risk of preeclampsia at their booking appointment, or have two or more moderate risk factors for preeclampsia are advised to take 75-150mg of aspirin daily from 12 weeks gestation onwards [80]. However, a recent meta-analysis of randomised trials including >18,000 women has shown that preventative treatment with aspirin only reduces the risk of preterm preeclampsia, and solely if treatment is started before 16 weeks gestation at a minimum dose of 100mg/day [81]. This meta-analysis did not find a reduction in the risk of developing term preeclampsia after aspirin treatment.

The NICE guidelines in the UK base the 'high-risk' status for developing preeclampsia on maternal characteristics such as nulliparity, previous obstetrical history and maternal age. However, more recently, the Aspirin for evidence-based Preeclampsia prevention (ASPREE)

trial that run between 2015 and 2016, identified high risk women through an algorithm, including maternal blood pressure, uterine artery doppler and serum biomarkers at 12 weeks gestation [82]. Women screened as high risk were then randomised into high dose (150mg) prophylactic aspirin treatment or placebo. The ASPRE trial found that aspirin treatment in the high risk group reduced the incidence of preterm preeclampsia by >60% compared to the placebo group [83]. Furthermore, the screening performance by the Fetal Medicine Foundation algorithm used in the ASPRE trial was far superior in identifying at-risk women than the NICE methods (75% versus 39% for preterm preeclampsia, respectively) [84]. Secondary analyses of this trial revealed that the beneficial effect may not apply to pregnancies affected by chronic hypertension [85], but no interaction was detected for maternal age, parity, BMI or (family) history of preeclampsia. This study highlights the need for the NICE guidelines to be updated, prioritising screening for preterm preeclampsia based on maternal characteristics plus biomarkers.

1.4.1.4 Pathophysiology

Preeclampsia is a pregnancy specific syndrome and has been named ‘the disease of theories’, reflecting the incomplete understanding of the pathophysiology [86]. As preeclampsia only occurs in the presence of a placenta, it is logical to link the placenta to the pathophysiology of the disease.

Factors originating from the placenta into the maternal circulation are thought to result in the maternal syndrome of preeclampsia [87]. Oxidative stress of the trophoblast is one of the hall marks of preeclampsia, as when the trophoblast is stressed it secretes e.g. pro-inflammatory cytokines and anti-angiogenic factors into the maternal circulation. One of the main stressors thought to disturb the trophoblasts is utero-placental malperfusion due to impaired remodelling of the spiral arteries [44]. During non-complicated pregnancies, the trophoblast will disrupt the smooth muscle and elastin layer of the wall of the spiral arteries and replace it by fibrinoid material [43].

Failed spiral artery remodelling has two consequences for placental perfusion [1]. Firstly, as the terminal segments are supposed to dilate into a funnel shape, this will reduced the velocity of the blood entering the intervillous space. If the remodelling is incomplete, maternal blood will enter the intervillous space at a much higher velocity if the spiral arteries do not dilate at the terminal end - a so called ‘hose effect’. The force that comes with those jet like streams is sufficient to drive apart villous branches and consequently intervillous

lakes will form. Simultaneously, the distance for the blood to decelerate and mix will be increased resulting in impaired materno-fetal oxygen exchange. It is also hypothesised that the microscopic damage to the villi can stimulate an inflammatory response due to the release of trophoblast segments [88]. Secondly, this remodelling takes place up to the inner third of the myometrium where there are hypercontractile segments of the spiral arteries located. Hence, if the spiral arteries fail remodelling, the smooth muscle layer will stay (partially) intact and therefore the arteries will retain their contractility. This will lead to intermittent perfusion of the intervillous space, exposing the placenta to ischaemia and reperfusion and subsequent reactive oxygen species production.

Furthermore, two major factors determining placental blood flow are the size of the placental bed, which depends on (i) the number of spiral arteries, and (ii) the depth of the spiral artery invasion in the peripheral placenta. It is known that the degree of trophoblast invasion is less in the periphery than the central placenta, leading to partial or absent remodelling of around 10% spiral arteries, even in non-complicated pregnancies [89]. In pregnancies affected by preeclampsia, complete spiral artery remodelling is greatly reduced in the central placental bed.

As in any other vascular disease, preeclampsia is characterised by an inflammatory response after ischemia and reperfusion, including cytokine releases, activation of apoptotic pathways and increased expression of anti-angiogenic factors (e.g. sFlt-1) [90]. sFlt-1 in turn inhibits pro-angiogenic factors such as PlGF and VEGF, impacting endothelial derived factors such as nitric oxide, prostacyclin, and endothelium-derived hyperpolarising factor. An imbalance in the endothelial derived factors can decrease endothelial smooth muscle relaxation and increase constriction, facilitating the characteristic hypertension [91]. Another way of assessing endothelial function is via flow-mediated dilation (FMD) (also see section 1.3.1). A meta-analysis investigating FMD at three time points during gestation showed that preeclamptic women had a lower FMD than normotensive women before the diagnosis of preeclampsia, at the time of diagnosis and postpartum [92]. As mentioned in section 1.3.1, NO is thought to mediate FMD and a reduction in NO synthesis could therefore contribute to the diminished relaxation. Women who will develop preeclampsia are shown to have three fold higher concentrations of asymmetric dimethylarginine, an endogenous inhibitor of endothelial NO synthase, compared to women with a non-complicated pregnancy [93].

Although the pathophysiology of preeclampsia is complex and extensive, Redman and Sargent tried to summarise the process [94]. In their hypothesis, the maternal immune system

appears to be less tolerant of the allogeneic trophoblasts, which causes a maldevelopment of the spiral arteries due to impaired invasion or function. Therefore, the second stage is characterised by poor placentation symbolised by small and muscular spiral arteries leading to high-resistance flow into the intervillous space and intermitted ischaemia. Subsequently, this causes endoplasmic reticulum stress and oxidative stress. In the final stage, a general maternal inflammatory response will develop because of the poor placentation and stressed placenta leading to endothelial dysfunction (Figure 1.5).

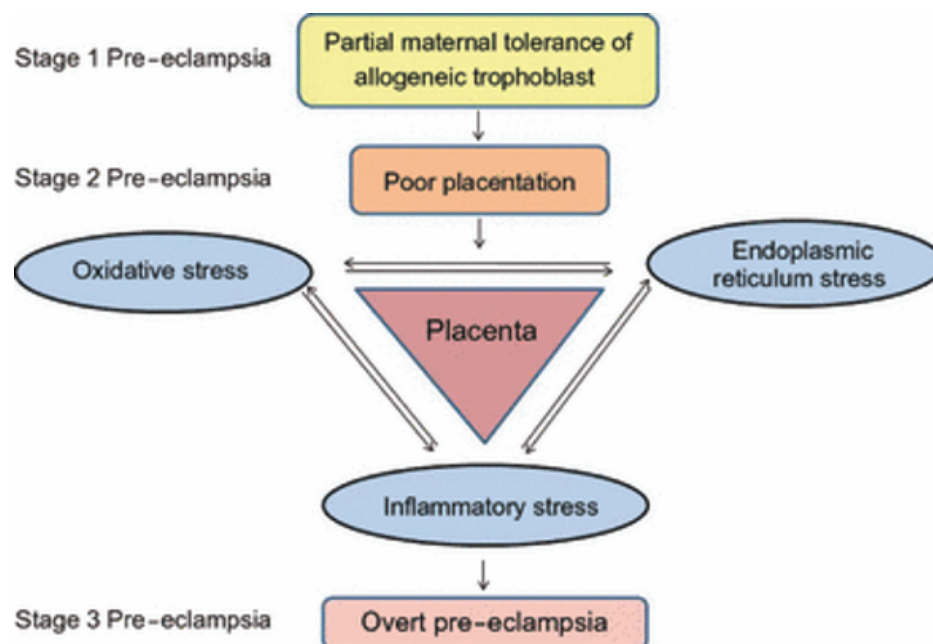


Fig. 1.5 Proposed three stage model for the development of preeclampsia. Adapted from Redman and Sargent [94].

Early and late preeclampsia often present with different haemodynamic states [52, 95]. Early preeclampsia is linked to failed placental vascular remodelling and is characterised by a high vascular resistance and reduced placental perfusion [95], whereas late preeclampsia is stronger linked to maternal constitutional factors [52]. Furthermore, although both early and late preeclampsia are associated with altered plasma levels of angiogenic factors such as sFLt-1 and PlGF, the differences are more pronounced in early preeclampsia [96–98].

1.4.2 Fetal growth restriction

1.4.2.1 Definition

Fetal growth restriction (FGR) occurs when a fetus does not reach its intrinsic growth potential. Fetal growth restriction and small for gestational age (SGA) are often used interchangeably, however FGR and SGA are in fact different. Small for gestational age is the statistical deviation of fetal size from a reference (often corrected for gestational age and fetal sex), whereas in FGR a fetus is pathologically small. It is important to distinguish SGA and FGR neonates, as FGR neonates are at a substantial risk of perinatal morbidity and mortality [99, 100].

Due to the major heterogeneity in the definition of FGR in the past decades, a Delphi panel was conducted in 2015 to reach consensus for the definition [101]. The definitions for early and late FGR based on the Delphi panel can be found in Table 1.3.

Early FGR (<32 weeks gestation)	Late FGR (>32 weeks gestation)
AC or EFW <3 rd centile OR absent end-diastolic flow in umbilical artery	AC or EFW <3 rd centile
OR	OR
AC/EFW <10 th centile combined with	AC/EFW <10 th centile combined with
UtA-PI > 95 th centile	AC/EFW crossing centiles >2 quartiles on growth centiles (non-customised)
UA-PI >95 th centile	UA-PI >95 th centile or CRP <5 th centile

Table 1.3 Criteria for the diagnosis of fetal growth restriction, as per Delphi panel consensus [101]. All definitions are in absence of congenital abnormalities. AC; abdominal circumference, CRP; cerebroplacental ratio, EFW; estimated fetal weight, FGR; fetal growth restriction, UA-PI; umbilical artery doppler pulsatility index, UtA-PI; uterine artery doppler pulsatility index.

A further way of trying to distinguish healthy and pathological pregnancies with SGA neonates is to adjust the estimated fetal weight or the birthweight percentile for maternal characteristics such as parity, ethnicity and maternal height as well as fetal sex and gestational age [102] and classify neonates born <10th centile using this correction as pathologically

small. This could lead to the identification of SGA neonates at higher risk of complications. However, the appropriateness of this correction is controversial as it is unclear if some of the variables that the birthweight centiles are corrected for lie on the causal pathway between maternal characteristics and adverse outcomes [103].

Screening for adequate fetal growth in the UK is currently done by symphysial-fundal height measurements from 24 weeks gestation. In the case of a height $<3^{rd}$ centile, women will be referred for fetal growth scans [58]. Routine ultrasound scanning after 24 weeks is not offered. A study by Sovio et al. showed that universal screening for SGA could identify a subset of FGR fetuses at risk for neonatal morbidity. However, for every correctly identified SGA neonate, about two additional results were false positive [104]. Clinical benefit of screening would therefore depend on benefits for the correctly identified FGR fetuses versus harm to the false positives.

1.4.2.2 Epidemiology

Due to the changing definition of FGR and the lack of consensus on a diagnosis before the Delphi panel in 2015, it is difficult to estimate the incidence of pathologically small neonates compared to constitutionally small neonates.

Since the introduction of the Delphi panel definition, incidences of FGR of 3.8-5.2% [105–107] have been reported in large prospective cohort studies using this classification. There is a big difference in incidence between early and late FGR; early FGR is reported in 0.5-1% of unselected singleton pregnancies, whereas late FGR is reported in ~5% [105].

Early detection of FGR is of high clinical priority, as it is one of the biggest risk factors for non-anomalous stillbirth and early intervention might prevent adverse outcomes. The risk of stillbirth in an FGR neonate is roughly five times greater if the FGR is not detected antenatally compared to pregnancies with detected FGR (32.0% v 6.2%, respectively) [100].

1.4.2.3 Risk factors

Similar to preeclampsia, the aetiology of fetal growth restriction is incompletely understood. However, multiple risk factors for delivering an SGA neonate are identified. Major risk factors for delivering an SGA neonate (relative risk >2), as defined by the Royal College

of Obstetrics and Gynaecology in the UK [108], can be found in Table 1.4

Maternal age >35 has been associated with an increased risk of delivering an SGA neonate, with the risk further increasing with age >40 years [109]. Smoking during pregnancy has been identified as a major risk factor [110], with an older meta-analysis estimating that 40% of fetal growth restriction is caused by maternal smoking [111]. However, one large cohort study found that if women ceased smoking before 15 weeks gestation, their risk of delivering an SGA neonate was not different from non-smokers, indicating that the effect might be reversible if a women stopped smoking in early pregnancy [112].

Maternal risk factors	Previous pregnancy complications	Current pregnancy complications
Age >40 years	Previous SGA neonate	Threatened miscarriage
Current smoker	Previous stillbirth	Preeclampsia
Daily vigorous exercise		Low maternal weight gain
Chronic hypertension		PAPP-A <0.4 MoM
Diabetes		
Renal disease		
Antiphospholipid syndrome		

Table 1.4 Major risk factors for the development of fetal growth restriction, as defined by the Royal College of Obstetrics and Gynaecology (UK). MoM; multiple of the median, PAPP-A; pregnancy-associated plasma protein A, SGA; small for gestational age neonate.

Women that previously gave birth to a growth restricted fetus are more than twice as likely to deliver an SGA neonate in a subsequent pregnancy [113, 114]. Having a placenta-related complication in past medical history, such as preeclampsia and stillbirth, also increases the risk of a subsequent SGA neonate [115], although much of the risk associated with a previous stillbirth seems to be linked to unacknowledged previous fetal growth restriction [116].

Additional to the major risk factors mentioned above, there are several weaker risk factors that could influence fetal weight. Maternal weight is classified as a minor risk factor for FGR, with a higher risk when prepregnancy BMI <20 or >25kg/m² [117, 118]. The shared background of maternal obesity and FGR will be further discussed in **section 1.4.1.**

Furthermore, little is known about the association between maternal obesity and subtypes of SGA, as SGA neonates can be divided into groups of constitutionally small or pathologically small neonates. I will investigate these relationships further in Chapter 6, as I investigate the

association between maternal prepregnancy BMI and the risk of delivering an SGA infant, when SGA was sub-grouped by the presence or absence of ultrasonic markers of FGR.

1.4.2.4 Pathophysiology

Fetal growth restriction can have many causes, such as congenital abnormalities, fetal genetic abnormalities or antenatal acquired infections. However, most cases that are not associated with these underlying factors are thought to arise from a compromised placental development and diminished adaptation of the uterine artery circulation [119].

As described in **section 1.3.1.4**, normal placental development depends on the adequate remodelling of the uterine circulation and its spiral arteries. As with preeclampsia, FGR is associated with deficiencies in trophoblast invasion, through malperfusion of the placenta [89]. Remodelling is seen as a continuous spectrum, with abnormal spiral arteries seen in healthy pregnancies, and vice versa. The causes of abnormal trophoblast invasion and subsequent spiral artery remodelling are vast, and more than one can be at play in one single pregnancy. For instance, excessive apoptosis in the placental bed can lead to a reduced number of trophoblasts [120], or failure of the trophoblast to penetrate the walls of the spiral arteries [121]. Furthermore, abnormal interactions with uterine natural killer cells could play a role [119]. Malperfusion of the placenta is a powerful inducer of oxidative stress, leading to damage to proteins and DNA, which can eventually lead to cell death, further inducing abnormal placentation [122].

There is biological variation in the presentation of FGR, as FGR itself is a heterogenous disease that can present alongside other perinatal complications. Furthermore, most studies investigating the placental pathology in FGR have not distinguished between SGA and true FGR, partly because of the lack of consensus on the diagnostic criteria. However, multiple macroscopic vascular anomalies have been associated with FGR. Placental thromboses and infarcts are amongst the most commonly found lesions in pregnancies complicated by FGR, with and without additional preeclampsia [123, 124]. Thromboses are found inside the intervillous space and can impair the nutrient exchange between mother and fetus. One case series found that thrombosis involving >50% of the placental bed is associated with a 70% incidence in FGR [125]. Placental infarcts can be the result of thromboses, leading to interrupted blood flow and eventually necrosis of the placental villi [126]. These macroscopic lesions are often presenting with abnormally high levels of alpha-fetoprotein and human chorionic gonadotrophin in the first trimester [127].

Type of lesion	Pathophysiology
Villous developmental defects (hypoplasia, dysmaturity, capillary dysplasia)	Under perfusion or malperfusion of intervillous space by maternal blood
Atherosclerosis of spiral arteries	Failure of spiral artery remodelling in placental basal plate
Villitis of unknown aetiology	Oxidative stress secondary to ischemia-reperfusion of intervillous space

Table 1.5 Common placental microscopic lesions found in fetal growth restriction. Adapted from Burton and Jauniaux [119].

Furthermore, various microscopic placental lesions have been linked to FGR. Many of these are non-specific and also found in uncomplicated pregnancies, but the extent and distribution of the lesion is thought to correlate with the severity of the complications (e.g. whether FGR presents in the context of preeclampsia, or the gestational age at onset) [127]. Table 1.5 gives an overview of the three commonly found microscopic lesions.

Lastly, as previously mentioned, FGR is a heterogeneous syndrome and can occur with other perinatal complications. Fetal growth restriction can be divided into subtypes by gestational age at presentation, where ≤ 32 week is labelled as early FGR and >32 weeks as late FGR. Late FGR can still display similar uteroplacental perfusion and vascular lesions as early FGR, but often with a less severe phenotype. There is significantly less overlap between FGR and preeclampsia at term than in the preterm period, suggesting FGR and preeclampsia might develop via distinct mechanisms at term [128, 129].

1.5 Maternal weight and preeclampsia & fetal growth restriction

1.5.1 Maternal obesity and preeclampsia & fetal growth restriction

1.5.1.1 Incidence of preeclampsia in maternal obesity

Maternal obesity is listed as a major risk factor for the development of preeclampsia, and increases the risk for this disease by approximately 2 to 3-fold [130]. The risk of preeclampsia is thought to increase with maternal prepregnancy BMI, even when a woman is not classified as overweight or obese [130–132], and doubles with every 5–7 kg/m² increase in prepreg-

nancy BMI [132].

A large study in the Danish National Birth Cohort aimed to estimate the population risk for preeclampsia associated with being overweight or obese, and found that 15–17% of the risk of early preeclampsia is attributable to a raised maternal prepregnancy BMI [133]. Furthermore, some population studies have suggested that the increase in incidence in preeclampsia over the last decades is in line with an increase in maternal obesity [61]. In the United States, maternal obesity was estimated to contribute to a 5-8 fold increased risk for severe preeclampsia in 2003, compared to women giving birth in 1980 [61]. Further evidence that obesity could play a causal role in the development of preeclampsia is provided by the fact that the risk of preeclampsia is lower after (extensive) weight loss [134].

1.5.1.2 Incidence of fetal growth restriction in maternal obesity

Although maternal obesity has been mainly associated with fetal overgrowth and a reduced risk of low birthweight, a few studies report a higher risk of FGR and risk of delivering an SGA neonate [118, 135]. Chen and colleagues reported a 17.6% incidence of SGA amongst Chinese obese women (classified as BMI $\geq 27.5 \text{ kg/m}^2$), cumulating into a relative risk of 2.73 compared to normal weight women. However, both studies reporting a positive association between low birthweight and maternal obesity defined FGR differentially: either as birth weight $< 10^{\text{th}}$ centile or < 2 standard deviations under the average weight for the gestational age. Neither took further markers of FGR as suggested by the Delphi panel into account.

1.5.1.3 Potential causal pathways

Obesity is one of the strongest risk factors for preeclampsia and there are many common background mechanisms that link obesity and preeclampsia [136, 137].

Firstly, obesity and preeclampsia are both associated with hyperinsulinemia and insulin resistance. Studies in a rat model showed that hyperinsulinemia is linked with shallower invasion of trophoblasts and altered nitric oxide synthesis [138]. Furthermore, hyperinsulinemia can raise blood pressure in pregnant rats independent of placental factors associated with preeclampsia [139, 140]. In humans, hyperinsulinemia and insulin resistance precede the clinical symptoms of preeclampsia [141].

Secondly, a state of low-grade inflammation has been reported in both conditions. Adipose tissue produces several inflammatory mediators that can act on the endothelium and are

thought to contribute to endothelial dysfunction in obesity and preeclampsia. C-reactive protein is one of the acute phase proteins strongly associated with inflammation and is found to be raised in obese individuals [142]. C-reactive protein is also found to be raised in women who later develop preeclampsia, before clinical symptoms are evident [143, 144]. Other proinflammatory cytokines that link obesity and preeclampsia are tumour necrosis factor- α [145] and interleukin-6 [146]. Bodnar and colleagues estimated that 30% of the effect of maternal prepregnancy BMI on the risk of preeclampsia was mediated by an increased inflammatory response [144].

Thirdly, endothelial dysfunction resulting from reduced nitric oxide availability has been suggested as a common mechanism between obesity and preeclampsia. Endothelial dysfunction is thought to underlie many of the clinical manifestations of preeclampsia, such as hypertension and oedema [86]. Endothelial dysfunction has also been reported in obese pregnancies; studies in pregnant obese women versus pregnant lean women show that obesity is associated with reduced endothelium-dependent vasorelaxation in skin arteries [147, 148]. Finally, endothelial dysfunction can also be found in previously preeclamptic women, independent of established risk factors for preeclampsia and more severe in women with recurrent preeclampsia [149].

Fourthly, obese women and preeclamptic women have similarities in placental histopathological changes. In term placentae, pre-gravid obesity was associated with a lower number, but larger diameter of villi suggesting villous immaturity [150]. Furthermore, term placentae from obese pregnancies display reduced vascular reactivity when exposed to vasoconstrictors [151]. When specifically examining the spiral artery conversion, there is a 'dose-dependent' increase in risk of abnormal spiral artery conversion with an increased maternal prepregnancy BMI [152], and poor spiral artery remodelling is one of the hallmarks of preeclampsia.

Lastly, the histological and molecular changes in the placentae of obese women can translate into a higher vascular resistance in the uteroplacental circulation. Chen et al. found an association between higher first trimester uterine pulsatility index (PI) and maternal prepregnancy BMI [153], whereas Kim and colleagues showed a similar pattern in the third trimester [154]. A uterine artery Doppler $>95^{th}$ centile (corrected for gestational age) is often used as a clinical marker of pathological development and can be used to monitor women at risk for abnormal fetal growth and preeclampsia [154]. Overweight and obese women have a higher incidence of a uterine artery doppler $>95^{th}$ centile at the end of the second [153] and third trimester [154]. However, little is known about the pattern of the physiological drop in

vascular resistance in the uterine or umbilical artery in obese women. In **Chapter 4**, I will investigate the maternal cardiovascular adaptation to pregnancy by examining the pattern of the physiological drop in the uterine and umbilical vasculature and compare this adaptation in women of different BMI categories.

The relationship between underlying mechanisms in maternal obesity and FGR is less clear than in preeclampsia. However, FGR is thought to arise from placental insufficiency. Impaired trophoblast invasion can be diagnosed through higher resistance in the uterine and umbilical arteries, and abnormal umbilical artery velocity waveforms are linked to FGR [155]. Sarno and colleagues found a higher vascular resistance in the umbilical artery at 32 weeks gestation in obese women compared to normal weight women, which could indicate a higher prevalence of placental insufficiency [156]. However, it is unclear if obesity is associated with other ultrasonic markers of fetal growth restriction such as uterine artery Doppler notching or a decreased middle cerebral artery Doppler.

1.5.2 Gestational weight gain and preeclampsia & fetal growth restriction

1.5.2.1 Suboptimal gestational weight gain and the incidence of preeclampsia

Several studies have shown an association between greater GWG and gestational hypertension [157, 158] or preeclampsia [158–160]. Furthermore, gestational weight loss was associated with a lower risk of developing preeclampsia in obese class II and III women in a large study in Germany [161]. Excessive GWG according to the IOM criteria is 1.5 times more prevalent in obese (56.4%) and overweight (59.1%) women compared to normal weight women (38.7%) according to the US Pregnancy Nutrition Surveillance 2009 [162].

Since the IOM criteria combine prepregnancy weight and weight gain during pregnancy in their recommendations, it is difficult to separate the effect of prepregnancy BMI and GWG on perinatal outcomes. Additionally, women that experience hypertension in pregnancy are more likely to develop oedema than normotensive pregnant women, which can result in greater GWG [163]. The Norwegian Fit for Delivery trial tried to untangle this relationship further and showed that women who develop preeclampsia gain more weight at any timepoint during gestation, but there was no difference in fat mass between groups at 30 and 36 weeks gestation. However, women who went on to develop preeclampsia gained an average of 3.5kg total body water more than women who did not develop preeclampsia. This weight gain was equal to the difference of total weight gained [164], suggesting that the oedema

could be the cause of the weight gain rather than the consequence. To further elucidate this relationship, the timing of weight gain should be considered and will be further discussed in **section 1.4.2.3**. Furthermore, I will investigate the association between timing of GWG and the risk of developing preeclampsia or delivering an SGA neonate in **Chapter 5**.

1.5.2.2 Incidence of fetal growth restriction in suboptimal gestational weight gain

The first IOM guidelines on GWG, released in 1990, were mainly focussed on the reduction of low birth weight by encouraging GWG. However, in guidelines published in 2009, it was recognised that excessive weight gain was associated with perinatal complications too, hence an upper and lower limit of GWG was suggested.

There is strong evidence for an association between weight gain less than the IOM guidelines and lower birthweight [165], and low weight gain and the risk of delivering an SGA neonate [166]. The incidence of delivering an SGA neonate when experiencing inadequate GWG ranges from between 15-30% for underweight women [158, 167] to 6-11% in obese women [158, 168]. Furthermore, there is moderately strong evidence that weight gain in excess of the IOM guidelines is associated with a higher birthweight [165]. The incidence of delivering an SGA neonate in women with excessive GWG ranges from 5-9% in underweight women [167, 168] to 4-6% in obese women [158, 169].

To my knowledge, no published study to date has investigated the association between GWG and FGR according to the Delphi panel definition, nor have there been studies that investigated the relationship between GWG and abdominal circumference growth velocity or resistance in the umbilical artery.

1.5.2.3 Timing of gestational weight gain and risk of obstetrical syndromes

Although the relationships between total GWG and preeclampsia (**section 1.4.2.1**) or birthweight (**section 1.4.2.2**) are well established, this approach might miss important gestational age-related differences in risk.

Studies investigating the timing of weight gain often classify the weight gain by trimester. For the relationship between timing of weight gain and birthweight, there is conflicting evidence on which trimester might be most influential. Some studies suggested that the second trimester is a key determinant of birthweight [170, 171], while others found a strong association between weight gain in the second and third trimester with birthweight [172, 173].

The difficulty when examining the relationship with first trimester weight gain is that studies often rely on self-reported prepregnancy weight and the reliability of self-reporting varies at the extremes of maternal weight. However, one large study recruited women in a premarital clinic and followed them up until birth of their first child. They found that weight gain up to 18 weeks gestation was most strongly associated with infant birthweight [174].

Research into patterns of GWG and preeclampsia is sparse. One study in women with gestational diabetes found that late excessive GWG is associated with severe preeclampsia (odds ratio (OR) 1.89, 95% CI (1.19-2.99)) [175] and a further study in the Generation R cohort reported that weight gain in the third trimester was associated with an increased risk of preeclampsia (OR 1.35 (95% CI 1.08,1.69), per standard deviation of change in gestational weight gain per week) [9]. However, caution needs to be exercised when linking third trimester GWG and preeclampsia as it is challenging to differentiate between cause and consequence. Preeclamptic women often develop oedema in the last stage of pregnancy which can in turn lead to (excessive) weight gain.

1.6 Long term consequences of maternal obesity

1.6.1 Maternal weight dynamics post-pregnancy and associated risk for subsequent pregnancies

Pregnancy itself is classified as a risk factor for developing obesity, which can in turn influence the outcomes of subsequent pregnancies and maternal health in later life. It is thought that lifestyle changes rather than biological changes lead to an increase in weight postpartum, which is labelled ‘postpartum weight retention’. A systematic review and meta-analysis found that postpartum weight steeply declines in the first three months after birth, and then continues to decrease up to 12 months postpartum [176]. A further meta-analysis that summarised the influence of GWG on long-term weight retention showed that women that gained more than the IOM recommendation retained 3 and 4.7kg more at 3 and 15 years postpartum, respectively, than women experiencing GWG within the IOM recommendations [177]. Lastly, a more recent meta-analysis showed that inadequate GWG was associated with 2.14kg less postpartum weight retention 21-years postpartum than adequate GWG according to the IOM guidelines [178].

Excessive GWG has been reported a risk factor for postpartum weight retention, and, as mentioned in **section 1.2.2.3.**, obese women are at greater risk of exceeding the IOM rec-

ommendations for GWG [25]. Furthermore, obese women are less likely to return to their prepregnancy weight compared to normal weight women [179]. Sumithran and colleagues found in a retrospective review of data from a tertiary hospital in Australia that substantial weight gain between two pregnancies (>4 BMI units) occurred in 7.5% of normal weight women, 10.5% of overweight women and 13.4% of obese women [180].

If associations between maternal prepregnancy weight and adverse perinatal outcomes are causal, weight retention between pregnancies can influence the risk of complications in a subsequent pregnancy. Outcomes associated with interpregnancy weight change include an increased risk of developing gestational diabetes [181–183], hypertensive disorders in pregnancy [181–184] and even stillbirth [183]. To further explore and summarise these associations, I conducted a systematic review and meta-analysis on the relationship between interpregnancy weight change and the risk of common perinatal complications in a subsequent pregnancy which can be found in **Chapter 2**.

Where maternal prepregnancy BMI and GWG are identified as risk factors for postpartum weight retention, breastfeeding is found to contribute to postpartum weight loss. An analysis in >36,000 women in the Danish National Birth Cohort showed that in women who breastfeed for the recommended 6 months, and had adequate weight gain during pregnancy, weight retention was eliminated by 6 months postpartum [185]. A meta-analysis summarising the association between the duration of breastfeeding and weight retention showed that breastfeeding for 6-12 months could significantly decrease weight retention compared to bottle feeding [186]. However, breastfeeding as a mechanism of reducing weight retention seemed to be most effective for women <30 years old, primiparous and/or with a normal prepregnancy BMI [186].

The postpartum period has been identified as a period where women are motivated to lose weight, with up to 81% of women reporting the plan to seek weight loss information postpartum [187]. However, the majority of women report that they never spoke about postpartum weight loss or physical activity with their healthcare providers [188]. Interventions that help women achieve their weight loss goals have been proposed and summarised [189–192]. These reviews conclude that interventions were successful, and a combination of dietary advice and physical activity with individualised (professional) support was the most effective. However, due to the heterogeneity of the timing of the interventions, they could not identify the most effective time in the post-partum period to intervene.

The current NICE guidelines in the UK identify the 6-8-week postpartum check-up as an opportunity to discuss a woman's weight [15]. Healthcare professionals are encouraged to give tailored and up to date advice on how to lose weight after childbirth, addressing a healthy diet and physical activity. Furthermore, women are encouraged to breastfeed and are reassured that losing weight does not impact on the quantity and quality of the breastmilk. Women who are overweight or obese should be offered a structured weight loss program and/or referral to a dietician [193].

1.6.2 Consequences for the offspring: Developmental Origins of Health and Disease

In addition to the immediate perinatal complications that are associated with prepregnancy weight, maternal obesity is seen as a major determinant of offspring health, in childhood and adult life [194]. The recognition that the intrauterine environment can have long term consequences on offspring health is labelled the 'Developmental Origins of Health and Disease (DoHaD)' hypothesis [195]. Although the causality is difficult to study in human observational studies, extensive work in animal models [196, 197] has linked maternal obesity with an increased risk of (offspring) obesity, adverse cardiovascular outcomes and even impaired neurodevelopment in offspring.

In humans, both maternal prepregnancy BMI and GWG are associated with an increased risk of childhood obesity [194, 198, 199]. Several studies suggest that this is not only the case with severe maternal prepregnancy obesity, but that maternal weight across the whole range is associated with offspring adiposity [200, 201]. Additionally, a longitudinal study in the Helsinki Birth Cohort suggests that maternal prepregnancy BMI is even related to offspring BMI at age ~60 [202]. When investigating the timing of the weight gain on offspring outcomes, the ALSPAC study suggested that weight gain <14 weeks gestation is associated with offspring adiposity [203].

A few large studies have investigated the relationship between maternal obesity and cardiometabolic outcomes in the child. A cohort study in Finland investigated the association between maternal prepregnancy weight and mortality rates from coronary artery disease. They found that for every standard deviation increase in mother's BMI, the hazard ratio (HR) for dying of coronary artery disease for (male) offspring was 1.24 (95% CI 1.10-1.39) [204]. Furthermore, a record-linkage study in the UK showed that maternal BMI >30 was associated with a higher all-cause mortality (HR 1.35 (95% CI 1.17-1.55)) and higher risk of

hospitalisation for a cardiovascular event (HR 1.29 (95% CI 1.06-1.57)) [205].

The increase in maternal obesity has been paralleled by an increased prevalence of neurodevelopmental problems in offspring [206]. A recent meta-analysis summarising the effects of maternal obesity found that children born to obese mothers are at higher risk of attention deficit disorder, autism spectrum disorders and cognitive delay [207]. Relative to children born to normal weight women, offspring of obese women had a 50% higher risk of any adverse neurodevelopmental outcome. Possible underlying mechanisms for this association are the higher inflammatory state in obese women affecting brain development, but mediation of this effect through gestational diabetes, preterm birth and/or asphyxia through birth trauma cannot be excluded [206, 208].

Epigenetic mechanisms are thought to underly the developmental programming of poorer offspring health in children born to obese mothers [194]. Epigenetic changes refer to alterations in the gene function, but without changes in the DNA code. DNA methylation is the epigenetic modification most studied in relation to maternal obesity and offspring adiposity. The largest study investigating maternal prepregnancy BMI and offspring DNA methylation found an increased methylation in offspring of obese women, compared to offspring of normal weight women [209], but no association between GWG and offspring methylation. Furthermore, a study comparing methylation in siblings born before and after their mother experiences significant weight loss through bariatric surgery found an improvement in the methylation levels of inflammatory and immune pathways, suggesting that maternal weight indeed influences offspring DNA methylation [210].

1.6.3 Consequences for the mother: Risk of cardiovascular disease

As mentioned in **section 1.5.1**, obese women and women with excessive GWG are at risk of postpartum weight retention and long-term obesity. Although all women are at risk of weight retention postpartum, obese women are shown to have a tendency to develop central fat retention [211]. In a study that examined the cardiometabolic profile of women in the first year after pregnancy found that women who did not lose weight between 3 and 12 months postpartum have a higher blood pressure, greater insulin resistance, higher low-density lipoprotein cholesterol [212] and lower high-density lipoprotein (HDL) cholesterol [213]. This decrease in HDL cholesterol associated with birth was still seen 10 years after birth [214]. Furthermore, women with excessive GWG have higher blood pressure 16 years after pregnancy, compared to women with adequate weight gain, even after adjustment for

maternal BMI [215].

Perinatal complications linked to obesity are also thought to put extra stress on the maternal metabolic system in the long term [216]. For instance, women diagnosed with gestational diabetes during pregnancy are at a higher risk of developing type II diabetes in the years postpartum. A meta-analysis estimated the relative risk of developing type II diabetes after gestational diabetes at 4 to 12-fold, compared to normoglycemic pregnancy [217]. A systematic review from 2016 found additional associations between type II diabetes and a raised fasting glucose during pregnancy and type II diabetes in women with an increased HbA1C during pregnancy [218]. Furthermore, gestational diabetes is thought to be positively associated with cardiovascular disease in later life, but this association could also be mediated largely by weight gain and unhealthy lifestyle in later life [219].

Obese women are also known to have a higher risk of preeclampsia (see **section 1.4.1.1**), which is known to be associated with a higher risk of cardiovascular disease in later life. It is hypothesised that this link comes from a shared cause or because preeclampsia could lead to vascular damage. A meta-analysis showed a higher risk of hypertension (RR 3.70 (95% CI 2.70-5.05)), ischaemic heart disease (RR 2.16 (95% CI 1.86 to 2.52)) and stroke (RR 1.81 (95% CI 1.45 to 2.27)) between 10-14 years postpartum [220]. Although most of the studies in the meta-analysis only adjusted for age, the largest study that included more than a million women found that the association between preeclampsia and future cardiovascular disease was independent from prepregnancy hypertension, diabetes mellitus and obesity [221]. The relative risk for all-cause mortality in the meta-analysis by Bellamy and colleagues was higher in women with a history of preeclampsia compared to women without preeclampsia (RR 1.49 (95% CI 1.05-2.14)) after 15 years follow up [220], and a consistent results was found in an analysis with an median follow up of 30 years (RR for all-cause mortality after preeclampsia versus no history of preeclampsia 2.1 (95% CI 1.8-2.5)) [222].

It is currently unknown if interventions to limit weight gain in pregnancy and the post-partum period are associated with improvements in cardiovascular risk factors in the mother. If interpregnancy weight loss could lead to a reduced incidence of perinatal complications in a subsequent pregnancy, then this might help to mitigate the risk of cardiovascular disease after e.g. preeclampsia. To further explore the possible benefits of interpregnancy weight change, I conducted a meta-analysis on the associations between interpregnancy weight loss and perinatal complications, which can be found in **Chapter 2**.

1.7 Aims and outline of the thesis

1.7.1 Objectives of the thesis

The aim of this thesis is to investigate the relationship between maternal weight dynamics and poor adaptation to pregnancy, manifesting as preeclampsia and fetal growth restriction. Figure 1.6 displays the framework that will be used to examine these associations. The objectives of this thesis are to:

1. Summarise the effects of interpregnancy weight gain and loss on the risk of perinatal complications
2. Evaluate the associations between obesity and physiological parameters of (cardiovascular) adaptation to pregnancy (Relationship A)
3. Investigate the effect of the timing of gestational weight gain on the great obstetrical syndromes (Relationship B)
4. Assess the association between obesity and fetal growth restriction (Relationship C)

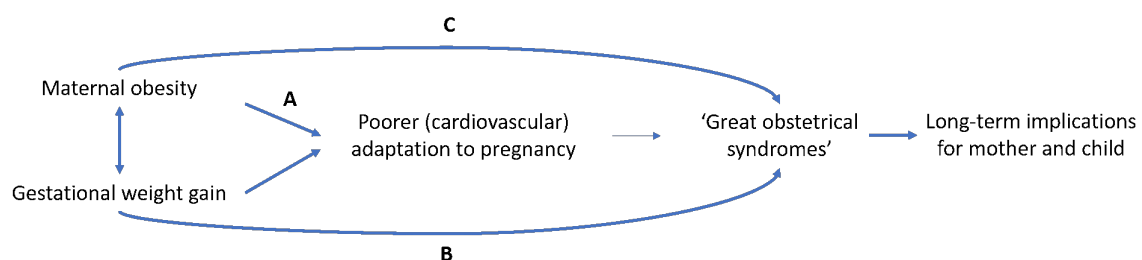


Fig. 1.6 Flowchart for evaluating the relationship between maternal prepregnancy BMI and/or gestational weight gain on (cardiovascular) adaptation to pregnancy and related perinatal outcomes.

1.7.2 Outline of the thesis

Chapter 2 investigates the relationship between interpregnancy weight change and the risk of perinatal complications in a subsequent pregnancy through a systematic review of the literature. **Chapter 3** describes the Pregnancy Outcome Prediction Study cohort dataset, which was used for the analysis in **Chapters 4, 5 and 6**. **Chapter 4** evaluates the impact of maternal obesity, fetal sex, and any interaction thereof on maternal cardiovascular adaptation to pregnancy, by assessing the physiological drop of uterine artery doppler pulsatility and umbilical artery doppler pulsatility index over gestation. **Chapter 5** assesses the impact

of the timing of GWG on the risk of developing preeclampsia and/or delivering an SGA neonate. **Chapter 6** determines the association between maternal prepregnancy BMI and ultrasonic markers of FGR in SGA neonates, to determine if obese women are at higher risk of delivering a pathologically small neonate rather than a constitutionally small neonate. **Chapter 7** summarises the findings of this thesis, explains the public health relevance and highlights strengths and limitations of the thesis. **Appendix A** lists the publications I have authored during my PhD. **Appendix B** shows the questionnaire all Pregnancy Outcome Prediction Study participants were asked to fill out at the 20 week scan. **Appendix C and D** provides the pre-specified analyses plans for the analyses conducted in **Chapter 5 and 6**.

Chapter 2

Effect of interpregnancy weight change on perinatal outcomes: systematic review and meta-analysis

This chapter has previously been published in BMC Pregnancy and Childbirth, including text and all figures. Contributions for each author can be found in the Acknowledgement section of this thesis.

Teulings NEWD, Masconi KL, Ozanne SE, Aiken CE, Wood AM. Effect of interpregnancy weight change on perinatal outcomes: systematic review and meta-analysis. BMC pregnancy and childbirth. 2019 Dec 1;19(1):386.

2.1 Chapter summary

Background: Although obesity is a well-known risk factor for adverse pregnancy outcomes, evidence is sparse about the effects of interpregnancy weight change on the risk of adverse perinatal complications in a subsequent pregnancy. The current study aims to assess the effect of interpregnancy weight change on the risk of developing gestational diabetes, preeclampsia, pregnancy induced hypertension, preterm birth, or delivering a large- or small for gestational age neonate.

Methods: Pubmed, Ovid Embase, ClinicalTrial.gov and the Cochrane library were systematically searched up until July 24th, 2019. Interpregnancy weight change was defined as the difference between prepregnancy weight of an index pregnancy and a consecutive pregnancy. Inclusion criteria included full text original articles reporting quantitative data about interpregnancy weight change in multiparous women with any time interval between consecutive births and the risk of any perinatal complication of interest. Studies reporting adjusted odds ratios and a reference group of -1 to +1 BMI unit change between pregnancies were harmonised by meta-analysis.

Results: Twenty-three cohort studies identified a total of 671,906 women with two or more consecutive pregnancies. Seven of these studies utilised a reference group of weight change between -1 and +1 BMI unit between pregnancies and were therefore included in the meta-analysis (280,672 women). Interpregnancy weight gain was consistently associated with a higher risk of gestational diabetes, preeclampsia, pregnancy induced hypertension and large for gestational age births. In contrast, interpregnancy weight loss was associated with a lower risk of delivering a large for gestational age neonate. The effect magnitude (relative risk) of interpregnancy weight gain on pregnancy induced hypertension or delivering a large for gestational age neonate was greater among women with a normal BMI in the index pregnancy compared to women with a starting BMI ≥ 25 kg/m².

Conclusion: These findings confirm that interpregnancy weight change impacts the risk of developing perinatal complications in a subsequent pregnancy. This provides evidence in support of guidelines encouraging women to achieve post-partum weight loss, as their risk of perinatal complications might be minimised if they return to their prepregnancy weight before conceiving again.

This analysis was prospectively registered with PROSPERO (CRD42017067326)

2.2 Background

Obesity is an increasing global health concern, with more than 1.9 billion adults worldwide being overweight [223] and approximately one in two US women of childbearing age now being considered overweight or obese [224]. Considerable evidence exists showing serious perinatal complications associated with obesity in pregnancy including gestational diabetes (GDM), preeclampsia (PE) and neonatal death [225]. There is also an increased risk of complications such as fetal growth restriction and preterm birth amongst underweight women [226]. Current National Institute for Health and Care Excellence (NICE) guidelines in the UK recommend that overweight or obese women are referred for weight loss support at the 6-8 week postnatal check-up [227] despite limited evidence to support widespread implementation of such health promotion strategies and of benefit for future pregnancy outcomes [228].

The current study aimed to systematically synthesise the published evidence on the associations between interpregnancy weight change and common perinatal complications for both mother and child including GDM, PE, pregnancy induced hypertension (PIH), preterm birth (PTB), and delivery of a large and small for gestational age neonate (LGA and SGA). Additionally, we compared the risk of these complications after interpregnancy weight change in women with a normal BMI and overweight or obese women, and where possible, we investigated the dose-response relationships.

2.3 Methods

2.3.1 Eligibility criteria, information sources, search strategy

The electronic databases PubMed, Ovid EMBASE, ClinicalTrials.gov and Cochrane Central were systematically searched until July 24th, 2019. The search strategy included terms relating to ‘interpregnancy’, ‘between pregnancy’, ‘weight change’ or ‘BMI’. These search terms were combined with the outcomes of interest (‘gestational diabetes’, ‘preeclampsia’, ‘pregnancy-induced hypertension’, ‘preterm birth’, ‘small for gestational age’ and ‘large for gestational age’) and synonyms of these outcomes (for full search string see Table 2.1). Furthermore, we cross-referenced selected papers for additional articles to include. The studies identified were uploaded onto Covidence, an online tool for screening of papers for systematic reviews (www.covidence.org). The review protocol was designed a priori and registered with PROSPERO under registration number CRD42017067326.

Table 2.1 Search strings

Interpregnancy OR Inter-pregnancy OR Inter pregnancy OR Between pregnancy OR Between pregnancies			
AND			
Weight change OR BMI OR Body Mass Index			
AND			
Small for gestational age, SGA, fetal growth restriction, foetal growth restriction, fetal growth retardation, foetal growth retardation, FGR, Intrauterine growth restriction, Intrauterine growth retardation, IUGR	OR	Large for gestational age, LGA	OR
		Preterm birth, Pre-term birth, Premature birth, Pre-mature birth, Preterm labour, Pre-term labour, Preterm labor, Prematurity	OR
		Gestational diabetes, Gestational diabetes mellitus, Pregnancy induced diabetes, Pregnancy-induced diabetes, GDM	OR
		Gestational hypertension, Pregnancy-induced hypertension, Pregnancy induced hypertension	OR
		Pre-eclampsia, preeclampsia	

2.3.2 Study selection

Studies were selected using the following predetermined inclusion criteria: [i] interpregnancy weight change reported in kilograms (kg), BMI units (kg/m^2) or percentage body weight change in multiparous women with any time interval between the consecutive births, [ii] any of the perinatal outcomes of interest in the subsequent pregnancy, and [iii] observational, cohort or case-controlled human study design with a sample size ≥ 50 , that were reported in English. When studies reported data from overlapping study populations, the study with the largest sample size was selected for inclusion. Information extracted from each study included country of research, study cohort name (if applicable), study period, sample size, study inclusion criteria, methods of weight reporting, definition of reference group, diagnostic criteria for perinatal outcomes and demographics that studies adjusted for. All study selection, full text screening, and data extraction was undertaken independently by two researchers, following PRISMA guidelines [229]. Disagreements were decided through a third opinion.

2.3.3 Data synthesis

Interpregnancy weight change was defined as the difference between prepregnancy weight in the index pregnancy, defined as the earliest recorded pregnancy, and prepregnancy weight in the subsequent pregnancy. Interpregnancy weight gain and loss were defined on two categorical scales; (i) for the meta-analysis we utilised categories of >1 BMI unit interpregnancy weight loss, BMI gain between 1-2 units, BMI gain between 2-3 units or BMI gain of more than 3 units and (ii) for the dose-response analysis we utilised a BMI gain of 0, 1, 2 or 3+ units. Crude odds ratios (calculated from studies providing relevant counts) and adjusted odds ratios for each outcome of interest were extracted from the selected publications.

To allow for heterogeneity between studies, a random effects meta-analysis was used to synthesize the odds ratios for weight change categories. To ensure a consistent reference group, only studies that employed a reference group of interpregnancy weight change between 1-unit weight loss and 1-unit weight gain were included. Heterogeneity was assessed using the I^2 statistic.

We conducted a separate analysis comparing interpregnancy weight change and the risk of developing adverse perinatal outcomes in women with a normal BMI ($<25\text{kg/m}^2$) versus women with an overweight BMI ($\geq 25\text{kg/m}^2$), at the start of their index pregnancy. To do so, adjusted odds ratios for both BMI categories were extracted from the publications and

summarised by random effects meta-analysis.

Dose-response relationships were assessed by plotting association measurements from studies providing multiple weight gain categories. Where ranges of BMI changes were reported, the midpoint of the category was used (e.g. 1.5 BMI units change for the category weight change between 1 and 2 BMI units).

Statistical analysis and graphical presentation were performed using the metafor package in R for Windows, version 3.4.2. [230].

2.3.4 Assessment of risk of bias

A sensitivity analysis was undertaken to assess potential impact of bias in individual studies by excluding studies that scored below 5 out of 9 points in the Newcastle-Ottawa Scale (NOS [231]) quality scoring assessment (Table 2.3). Furthermore, leave-one-study-out analyses were conducted to identify whether one study leveraged the overall effect size estimate.

2.4 Results

2.4.1 Study selection

We identified and screened 4,500 unique publications and included 194 articles for full text review (Figure 2.1). A total of 27 studies were eligible for inclusion. Three studies were excluded due to overlapping study populations [232–234] and one was excluded because of a sample size <50 women [235]. From the remaining 23 studies selected to take forward, a total of 671,906 women were identified for inclusion in the review (Table 2.2). Eighteen studies included only nulliparous women at the index pregnancy. The proportion of women older than 35 years varied between studies from 3% to 33%. All studies were conducted in Western populations, although this was not an inclusion criterion. Seven studies, comprising of 280,672 women, were included in the meta-analysis.

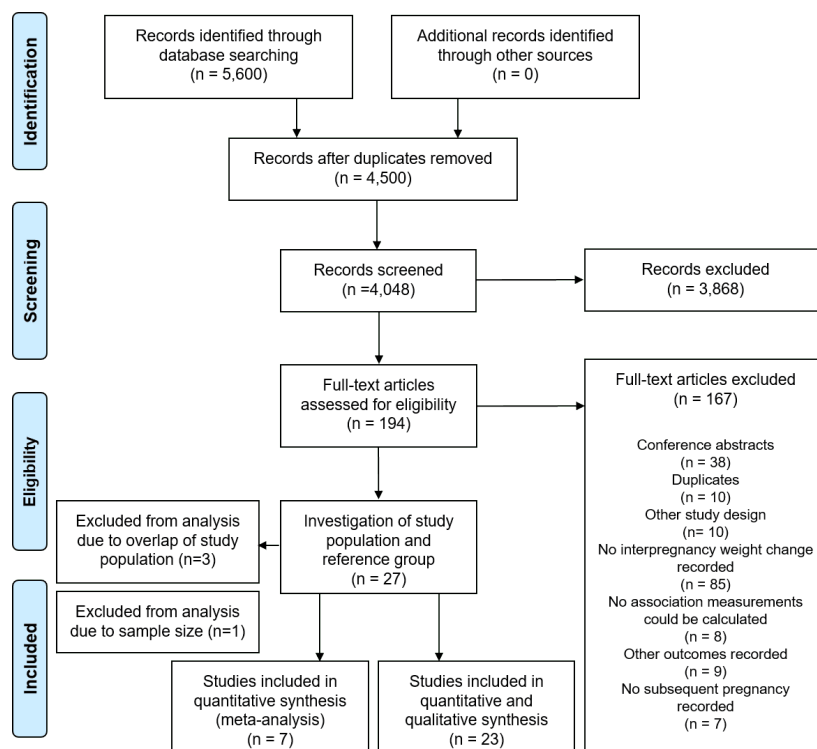


Fig. 2.1 Flow diagram of studies reporting on interpregnancy weight change and perinatal outcomes of interest.

Table 2.2 Studies that evaluated the associations between interpregnancy weight change and perinatal complications

Author and publication year	Included in MA?	Country	Study cohort (if applicable)	Study period	Sample size	Inclusion criteria	Reported weight	Reference group	Diagnostic criteria	Confounders adjusted for
Bogerts et al. 2013 [236]	Yes	Belgium	Study Centre for Perinatal Epidemiology database	2009-2011	7,897	Two first consecutive births	Self-reported weight and height	± 1 BMI unit	GDM: not clarified PIH: not clarified	Prepregnancy BMI at first pregnancy, interpregnancy interval, gestational age at first delivery, maternal age, gestational weight gain, complications at first pregnancy (GDM, PIH, induction of labour, CS, malformations and mortality)
Bender et al. 2018 [237]	No	USA	Hospital of Pennsylvania retrospective cohort	2005-2010	537	Singleton livebirth followed by consecutive pregnancy	Weight measured at first antenatal visit, self-reported height	Stable BMI category	GDM: Carpenter-Coustan criteria for the 3-hour glucose tolerance test PIH: Task Force on Hypertension in Pregnancy PTB: <37 weeks	Maternal age, GDM in prior pregnancy, prepregnancy BMI category
Benjamin et al. 2019 [238]	No	USA	Texas linked siblings pair	2005-2012	2,481	Birth certificates linked with older live birth, singleton sibling	Self-reported weight and height	0 to <1 BMI units weight gain	SGA: Not reported LGA: Not reported PTB: Not reported	Prepregnancy BMI at sibling pregnancy, ethnicity, smoking status, gestational weight gain, height, maternal age and education

(Continued) Studies that evaluated the associations between interpregnancy weight change and perinatal complications.

Author and publication year	Included in MA?	Country	Study cohort (if applicable)	Study period	Sample size	Inclusion criteria	Reported weight	Reference group	Diagnostic criteria	Confounders adjusted for
Chen et al. 2009 [239]	No	USA	Collaborative Perinatal Project	1959-1966	1,892	Singleton livebirth followed by consecutive singleton pregnancy	Self-reported weight and height	-0.32 to 1.48 BMI units	PTB: <37 weeks	Maternal age, research centre, race, smoking status, socio-economic index, marital status and interpregnancy interval
Cheng et al. 2007 [240]	No	USA	Missouri maternally linked cohort	1989-1997	14,114	Second-born SGA infants	Self-reported weight and height	No change in BMI	SGA: <10 th percentile	Not reported
Crosby et al. 2017 [241]	No	Ireland	Follow up of ROLO study	2007-2015	280	Secundigravida who previously gave birth to macrosomic (>4.0kg) baby	Weight and height measured at first antenatal visit	No inter-pregnancy weight gain (not further specified)	GDM: Not specified	No adjusted model available
Ehrlich et al. 2011 [181]	Yes	USA	Kaiser Permanent Northern California	1996-2006	22,351	Women without recognised diabetes before pregnancy, first and second live born singletons	Measured by clinician at time of alpha fetoprotein test (mean GA 16.9 weeks)	± 1.0 BMI unit	GDM: According ADA criteria	Maternal age, race, ethnicity, place of birth, GDM status in first pregnancy, prepregnancy BMI in first pregnancy, gestational age, interpregnancy interval

(Continued) Studies that evaluated the associations between interpregnancy weight change and perinatal complications.

Author and publication year	Included in MA?	Country	Study cohort (if applicable)	Study period	Sample size	Inclusion criteria	Reported weight	Reference group	Diagnostic criteria	Confounders adjusted for
Getahun et al. 2007 [242]	No	USA	Missouri vital record system	1989-1997	136,884	No history of preeclampsia in index pregnancy, delivering second baby	Self-reported weight and height	Normal BMI (18.5-24.9 kg/m ²) in both pregnancies	PE: hypertension and proteinuria beyond 20 th week gestation in women normotensive before pregnancy	Maternal age, race, education, marital status, prenatal care, smoking status and interpregnancy interval
Getahun et al. 2007 [243]	No	USA	Missouri vital record system	1989-1997	146,227	First two consecutive singleton pregnancies	Self-reported weight and height	Normal BMI (18.5-24.9 kg/m ²) in both pregnancies	LGA: $\geq 90^{\text{th}}$ percentile	Maternal age, race, education, marital status, prenatal care, smoking status, alcohol during pregnancy, marital status and interpregnancy interval
Glazer et al. 2004 [244]	No	USA	Washington State Longitudinal Births Database	1992-1998	4,102	Non-diabetic women with weight ≥ 200 lbs with ≥ 2 singleton births	prepregnancy weight from birth certificate, unspecified how measured	± 10 lb	GDM: not clarified	Maternal age, gestational weight gain in index pregnancy and gestational weight gain during subsequent pregnancy

(Continued) Studies that evaluated the associations between interpregnancy weight change and perinatal complications.

Author and publication year	Included in MA?	Country	Study cohort (if applicable)	Study period	Sample size	Inclusion criteria	Reported weight	Reference group	Diagnostic criteria	Confounders adjusted for
Hoff et al. 2009 [245]	No	USA	Missouri birth certificates	1995-2004	1,035	First two consecutive singleton pregnancies in overweight women	prepregnancy weight from birth certificate, unspecified how measured	Overweight BMI (25.0-29.9 kg/m ²) in both pregnancies	PIH : not clarified PTB : <37 weeks	No adjusted model available
Jain et al. 2013 [246]	No	USA	Missouri vital record system	1998-2005	10,444	First two consecutive singleton pregnancies with a BMI ≥ 30 at index pregnancy	Self-reported weight and height	± 2 BMI units	SGA : <10th percentile LGA : < 90th percentile	Maternal age, race, marital status, education, socioeconomic status, obesity status in first pregnancy, gestational weight gain, smoking, PE, prenatal care, previous SGA or LGA birth, DM, hypertension, renal or cardiac disease
Knight-Agarwal et al. 2016 [247]	Yes	Australia	Birth Outcome System	2008-2013	14,875	Women of all parity with subsequent pregnancies	Weight and height recorded at first antenatal visit (mean GA not reported)	± 1 BMI unit	GDM : not clarified	Maternal age, parity, country of birth, smoking status

(Continued) Studies that evaluated the associations between interpregnancy weight change and perinatal complications.

Author and publication year	Included in MA?	Country	Study cohort (if applicable)	Study period	Sample size	Inclusion criteria	Reported weight	Reference group	Diagnostic criteria	Confounders adjusted for
Kruse et al. 2015	No	Denmark	NA	2009-2013	72	Primiparas with a history of GDM	Unspecified how weight was recorded	No change in BMI units	GDM: $\geq .0$ mmol/L blood glucose 2h after OGTT	No adjusted model available
Lynes et al. 2017 [182]	Yes	USA	NICHD Consecutive Pregnancy Study	2002-2010	46,521	First two consecutive singleton births	Unspecified how weight was recorded	± 1 BMI unit	GDM: not clarified PIH: ± 140 mmHg systolic and ± 90 mmHg diastolic without proteinuria PE: ± 140 mmHg systolic and ± 90 mmHg diastolic with proteinuria	Maternal race, interpregnancy interval, maternal age, marital status, smoking status, alcohol use during second pregnancy, prepregnancy BMI, complication in first pregnancy (GDM, PE, PIH)
McBain et al. 2016 [248]	No	Australia	Women's and Children's Health Network	2000-2012	5,371	First and second consecutive deliveries	BMI units recorded at first antenatal visit (before GA 15 weeks)	± 2 BMI units	GDM: not clarified PTB: not clarified SGA: <10th centile LGA: ≥ 90 th centile	Maternal age, socioeconomic status, prepregnancy BMI in first pregnancy, smoking status, race, interpregnancy interval, first pregnancy outcome (GDM, PIH, birth method, LGA and SGA)

(Continued) Studies that evaluated the associations between interpregnancy weight change and perinatal complications.

Author and publication year	Included in MA?	Country	Study cohort (if applicable)	Study period	Sample size	Inclusion criteria	Reported weight	Reference group	Diagnostic criteria	Confounders adjusted for
Pole et al. 1999 [249]	No	Canada	Nova Scotia Atlee Perinatal Database	1988-1996	19,932	Two or more singletons	Not stated	$\pm 3\%$ weight	GDM: two abnormal glucose values on a GTT according to Joslin Clinic or O'Sullivan criteria PIH: BP ≥ 90 mmHg diastolic, twice in 24h	Prepregnancy weight (in lbs) of index pregnancy, gestational age, marital status, previous CS, maternal age, gestational weight gain, GDM in previous pregnancy
Simonsen et al. 2013 [250]	No	USA	Maternally linked Utah birth and fetal records	1989-2007	8,468	First three singleton live births	prepregnancy BMI from birth certificate (mean GA not reported)	BMI category unchanged	PTB: ≥ 20 and < 37 weeks	Maternal age, ethnicity, gestational weight gain, father on birth record, interpregnancy interval, subtype of previous PTB, gestational age at previous PTB, fetal death or anomaly in history
Sorbye et al. 2017 [251]	Yes	Norway	Medical Birth Registry of Norway	2006-2014	24,198	First and second delivery without GDM in index pregnancy	Unspecified how weight was recorded	± 1 BMI units	GDM: fasting glucose < 7.0 mmol/l and serum glucose after OGTT ≥ 7.8 mmol/l	Maternal age, country of birth, maternal education, smoking status, interpregnancy interval and year of delivery

(Continued) Studies that evaluated the associations between interpregnancy weight change and perinatal complications.

Author and publication year	Included in MA?	Country	Study cohort (if applicable)	Study period	Sample size	Inclusion criteria	Reported weight	Reference group	Diagnostic criteria	Confounders adjusted for
Villamor et al. 2006 [183]	Yes	Sweden	Swedish Birth Register	1992-2001	151,025	First and second consecutive singleton births	BMI units recorded at first antenatal visit (mean GA not reported)	±1 BMI units	GDM: ICD-9 648W, ICD-10 O244 PE: ICD-9 642E-642H, ICD-10 O11 and O14 PIH: ICD-9 642D and 642X, ICD-10 O13 LGA: ≥ 2 SD above mean birthweight	Prepregnancy BMI in first pregnancy, height, interpregnancy interval, maternal age, country of birth, education, year of delivery, smoking status
Wallace et al. 2014 [184]	Yes	Scotland	Aberdeen Maternity and Neonatal Databank	1986-2007	12,740	First two consecutive births	Weight and height recorded at first antenatal visit (mean GA not reported)	±1 BMI units	PE: ISSHP definition PIH: ISSHP definition PTB: <37 weeks SGA: <10 th h percentile LGA: $\geq 90^{\text{th}}$ percentile	Prepregnancy BMI in first pregnancy, height inter-delivery interval, maternal age, year of delivery, smoking status, gestational age and fetal gender at second pregnancy

(Continued) Studies that evaluated the associations between interpregnancy weight change and perinatal complications.

Author and publication year	Included in MA?	Country	Study cohort (if applicable)	Study period	Sample size	Inclusion criteria	Reported weight	Reference group	Diagnostic criteria	Confounders adjusted for
Wallace et al. 2016 [252]	No	Scotland	Aberdeen Maternity and Neonatal Databank	1986-2013	24,520	First two consecutive births and the same perinatal complication in both pregnancies	Weight and height recorded at first antenatal visit (mean GA not reported)	± 2 BMI units	PTB: <37 weeks PE: ISSHP definition PIH: ISSHP definition SGA: <10th percentile LGA: $\geq 90^{th}$ percentile	Prepregnancy BMI in first pregnancy, year of delivery, height, inter-delivery interval, maternal age, smoking status, gestational age and fetal sex at first and second pregnancy
Ziauddeen et al. 2019 [253]	Yes	England	Birth registry at Southampton Hospital	2003-2017	15,940	First two consecutive singleton live-birth pregnancies	Weight recorded at first antenatal visit; height self-reported	± 1 BMI unit	LGA: >90 th percentile for GA	Baseline BMI, maternal age, education level, infertility treatment, smoking status, employment status, GDM in current pregnancy and interpregnancy interval

To ensure a consistent reference group, only studies that employed a reference group of interpregnancy weight change between 1-unit weight loss and 1-unit weight gain were included. ADA; American Diabetes Association, BP; blood pressure, GDM, gestational diabetes; ICD; International Classification of Disease, ISSHP; International Society for the Classification of Hypertension in Pregnancy, MA; meta-analysis, NA; not applicable, OGTT; Oral Glucose Tolerance Test, PE, preeclampsia; PIH; pregnancy induced hypertension; PTB, preterm birth; SGA, small for gestational age; LGA, large-for gestational age; BMI, body mass index; GA, gestational age; CS, caesarean section; DM; diabetes mellitus

2.4.2 Synthesis of results

Interpregnancy weight gain of between 1-2 BMI units was associated with a 51% higher risk of developing GDM (adjusted odds ratio (aOR) 1.51 95% Confidence interval (CI) [1.22-1.80], $I^2=70.1\%$), whereas an increase of 2-3 or more than 3 BMI units was associated with an 81% and 137% higher risk (aOR 1.81 [1.20-2.41], $I^2=88.4\%$ and aOR 2.37 [1.50-3.34], $I^2=91.0\%$ respectively) (Figure 2.2).

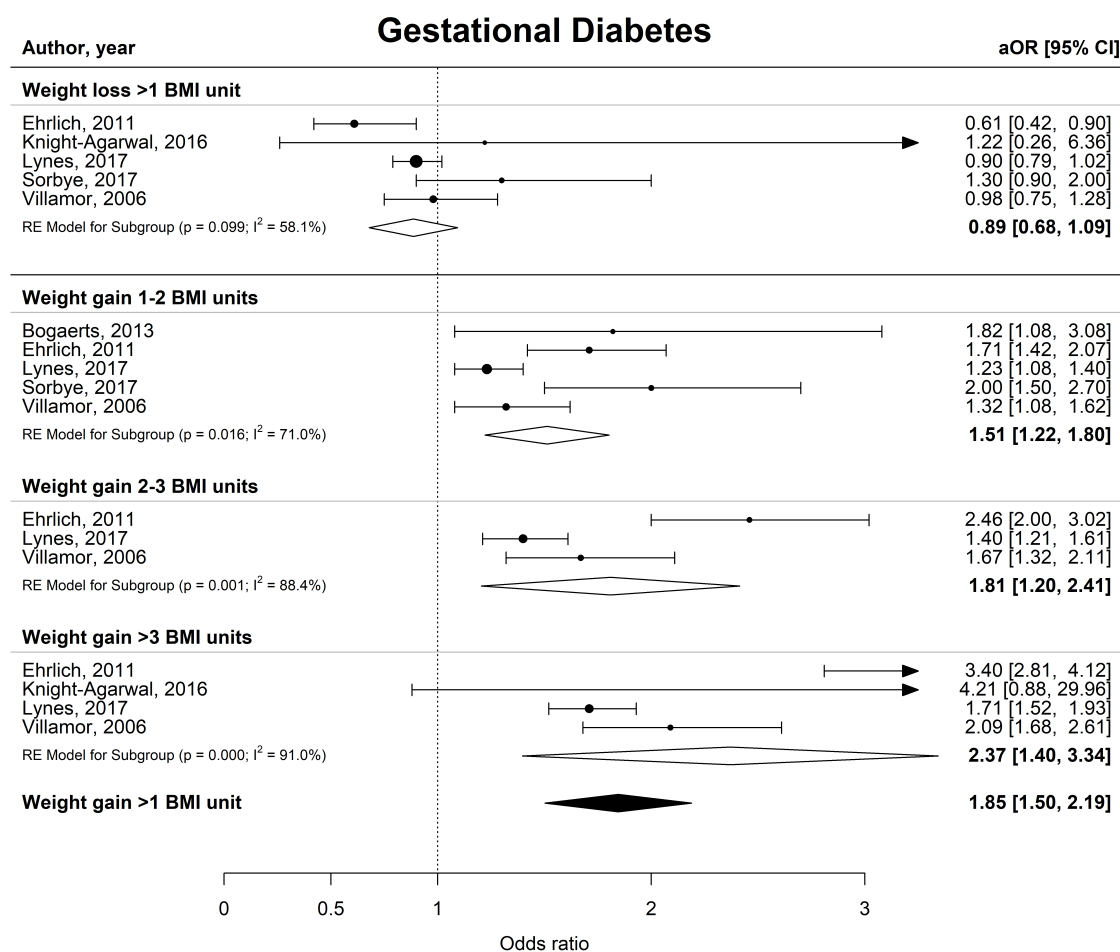


Fig. 2.2 Forest plot from random effects meta-analysis showing the association between interpregnancy weight change and the risk of developing gestational diabetes in subsequent pregnancy. All adjusted odds ratios are relative to the reference category of interpregnancy weight change between -1 and +1 BMI units. BMI, body mass index (in kg/m^2); aOR, adjusted odds ratio; CI, confidence interval.

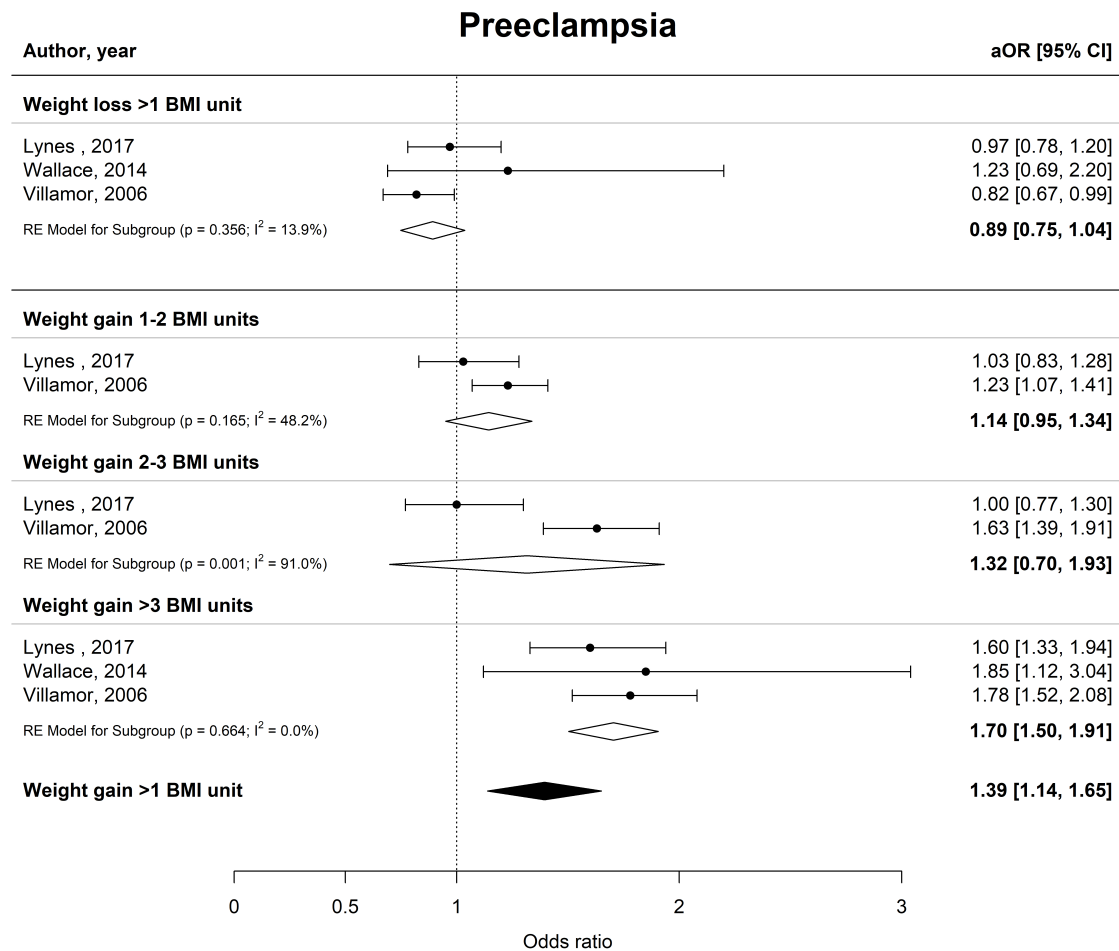


Fig. 2.3 Forest plot from random effects meta-analysis showing the association between interpregnancy weight change and the risk of developing preeclampsia in subsequent pregnancy. All adjusted odds ratios are relative to the reference category of interpregnancy weight change between -1 and +1 BMI units. BMI, body mass index (in kg/m^2); aOR, adjusted odds ratio; CI, confidence interval.

Furthermore, interpregnancy weight gain of more than 3 BMI units was associated with a higher risk of PE or PIH (aOR 1.70 [1.50-1.91], $I^2=0.0\%$ and aOR 1.71 [1.51-1.91] $I^2=0.0\%$ respectively) (Figure 2.3 and Figure 2.4). The association between interpregnancy weight change and the risk of delivering an LGA neonate could only be estimated for a weight gain >3 BMI units, and showed a 63% higher risk (aOR 1.63 [1.30-1.97], $I^2=85.6\%$) (Figure 2.5).

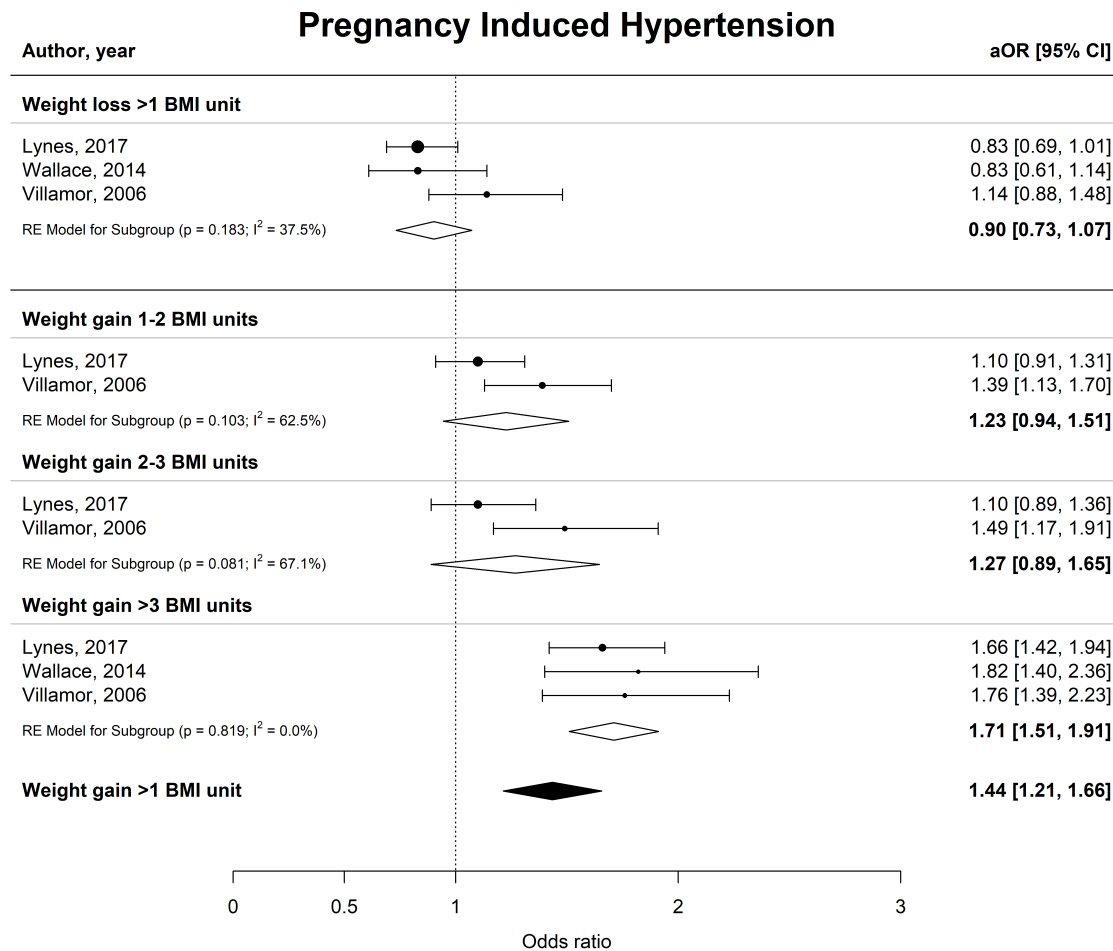


Fig. 2.4 Forest plot from random effects meta-analysis showing the association between interpregnancy weight change and the risk of developing pregnancy induced hypertension in subsequent pregnancy. All adjusted odds ratios are relative to the reference category of interpregnancy weight change between -1 and +1 BMI units. BMI, body mass index (in kg/m²); aOR, adjusted odds ratio; CI, confidence interval.

In contrast, interpregnancy weight loss of >1 BMI unit was associated with a lower risk of delivering an LGA neonate, (aOR 0.79 [0.58-0.99], $I^2=86.1\%$) (Figure 2.5), but there was no conclusive evidence of association of interpregnancy weight loss with the risk of developing GDM, PE or PIH (Figure 2.2, 2.3 and 2.4). There was an insufficient number of studies to conduct a meta-analysis on adjusted odds ratios for the outcomes of SGA and PTB. A meta-analysis combining the crude odds ratios (cOR) rather than adjusted ratios showed a significantly higher risk of developing PE (cOR 1.31 [1.09-1.53], $I^2=75.1\%$), but

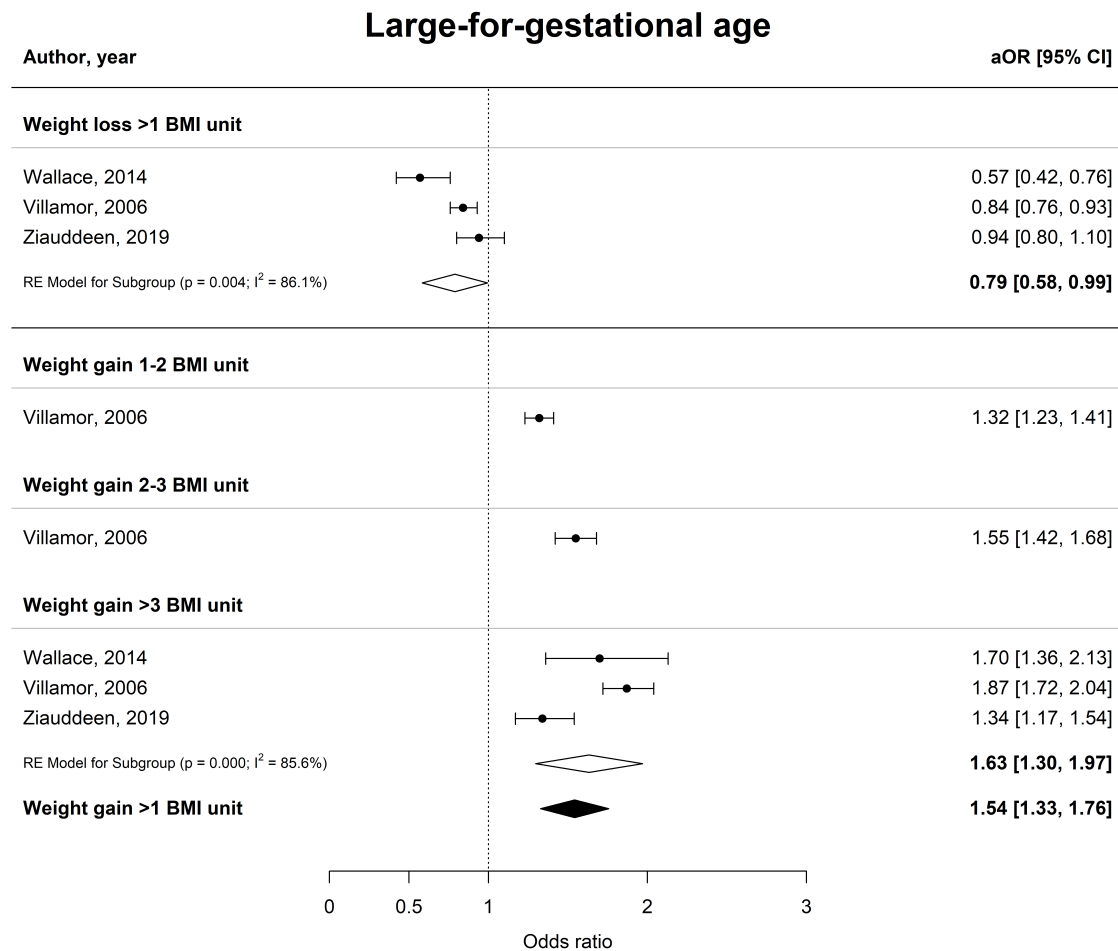


Fig. 2.5 Forest plot from random effects meta-analysis showing the association between interpregnancy weight change and the risk of delivering a large for gestational age neonate in subsequent pregnancy. All adjusted odds ratios are relative to the reference category of interpregnancy weight change between -1 and +1 BMI units. BMI, body mass index (in kg/m^2); aOR, adjusted odds ratio; CI, confidence interval.

showed similar results for the association between interpregnancy weight gain and the risk of developing GDM, PE or PIH (Figure 2.6 for interpregnancy weight loss and Figure 2.7 for weight gain).

For the outcomes of SGA and PTB, meta-analyses of crude odds ratios showed interpregnancy weight loss of >1 BMI unit was associated with a higher risk of delivering a SGA neonate or delivering preterm (cOR 1.53 [1.35-1.71], $I^2 = 0.0\%$ and cOR 1.45 [1.21-1.69],

$I^2=26.7\%$] respectively), but there was no evidence of association with interpregnancy weight gain (Figures 2.6 and 2.7).

Figures 2.8, 2.9, 2.10 show the odds ratios for the risk of developing an adverse perinatal outcome after interpregnancy weight gain, stratified by BMI category in the index pregnancy (normal weight; BMI <25 kg/m² versus overweight; BMI ≥ 25 kg/m²). Women with a normal weight at the start of the index pregnancy had a higher risk of developing GDM after interpregnancy weight gain >3 BMI units (aOR 4.36 [2.29-6.44], $I^2=81.6\%$) compared to women with an overweight BMI (aOR 2.26 [1.40-3.12], $I^2=74.4\%$) (Figure 2.8). Similarly, women with a BMI <25 kg/m² were at higher risk of delivering a LGA neonate after interpregnancy weight gain >3 BMI units than women with BMI ≥ 25 kg/m² (aOR 1.80 [1.24-2.35], $I^2=87.2\%$ versus aOR 1.50 [1.35-1.66], $I^2=0.0\%$ respectively) (Figure 2.9). Women with a normal BMI at the start of their index pregnancy were at higher risk of developing PIH in a subsequent pregnancy after interpregnancy weight gain of 2-3 BMI (aOR 1.60 [1.04-2.16], $I^2=54.6\%$) and >3 BMI units (aOR 2.21 [1.81-2.60], $I^2=0.0\%$), compared to women with an overweight BMI (2-3 units gain; aOR 0.95 [0.73-1.17], $I^2=0.0\%$, >3 units gain; aOR 1.37 [1.16-1.59], $I^2=0.0\%$) (Figure 2.10). We did not find differential effects of interpregnancy weight loss between women with a normal BMI and women with an overweight BMI on the risk of developing GDM, PIH or delivering an LGA neonate.

There was an approximate log-linear association between interpregnancy weight gain and the risk of developing GDM, PE or PIH and delivering a LGA neonate (Figure 2.11).

2.4.3 Risk of bias of included studies

After assessing the study selection criteria, comparability of cases and controls and outcome assessments through the NOS, we identified four studies of poor quality (NOS score <5 , Table 2.3). However, as these studies did not employ a reference group of ± 1 BMI unit, they were already excluded from the meta-analyses. Leave-one-out-analyses showed that removing the study by Villamor et al. [183] made the association between GDM and interpregnancy weight change of 2-3 or >3 BMI units not significant, possibly due to the large sample size ($>150,000$) and hence wide confidence intervals on removal of this study. We did not find evidence that the results for the outcomes PE or PIH were driven by one study. For the outcome of delivering an LGA neonate, leave-one-out analyses could not be conducted due to only two studies being included in the meta-analysis.

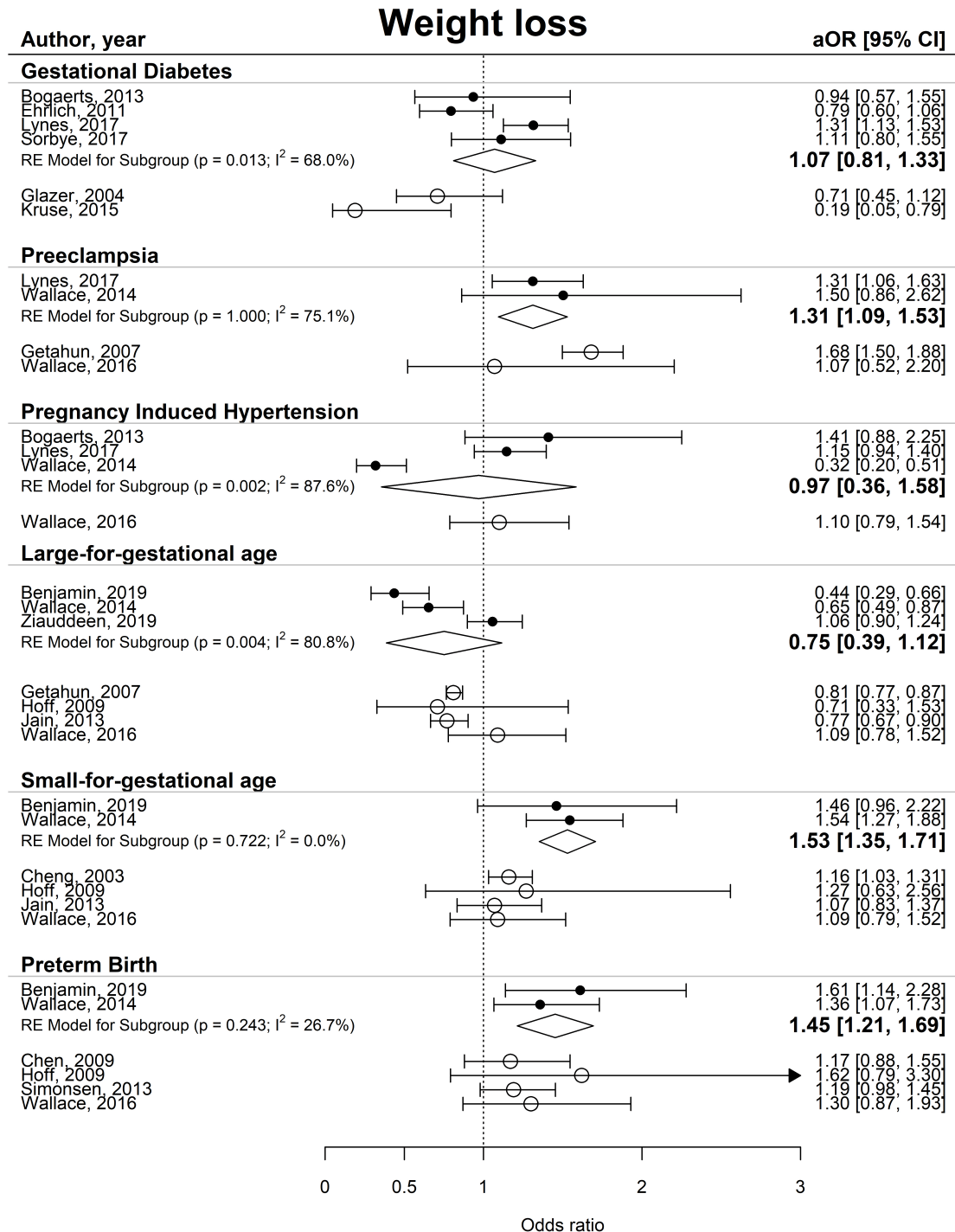


Fig. 2.6 Forest plot from random effects meta-analysis showing the crude odds ratios for the association between interpregnancy weight loss and the risk for perinatal outcomes of interest. Black, solid dots represent studies with reference group of interpregnancy weight change between -1 and +1 BMI unit and are therefore included in the meta-analyses. White, open dots represent studies not using a reference group of interpregnancy weight change between 1-unit weight loss and 1-unit weight gain and are visually displayed but not included in the meta-analysis. cOR, crude odds ratio; CI, confidence interval.

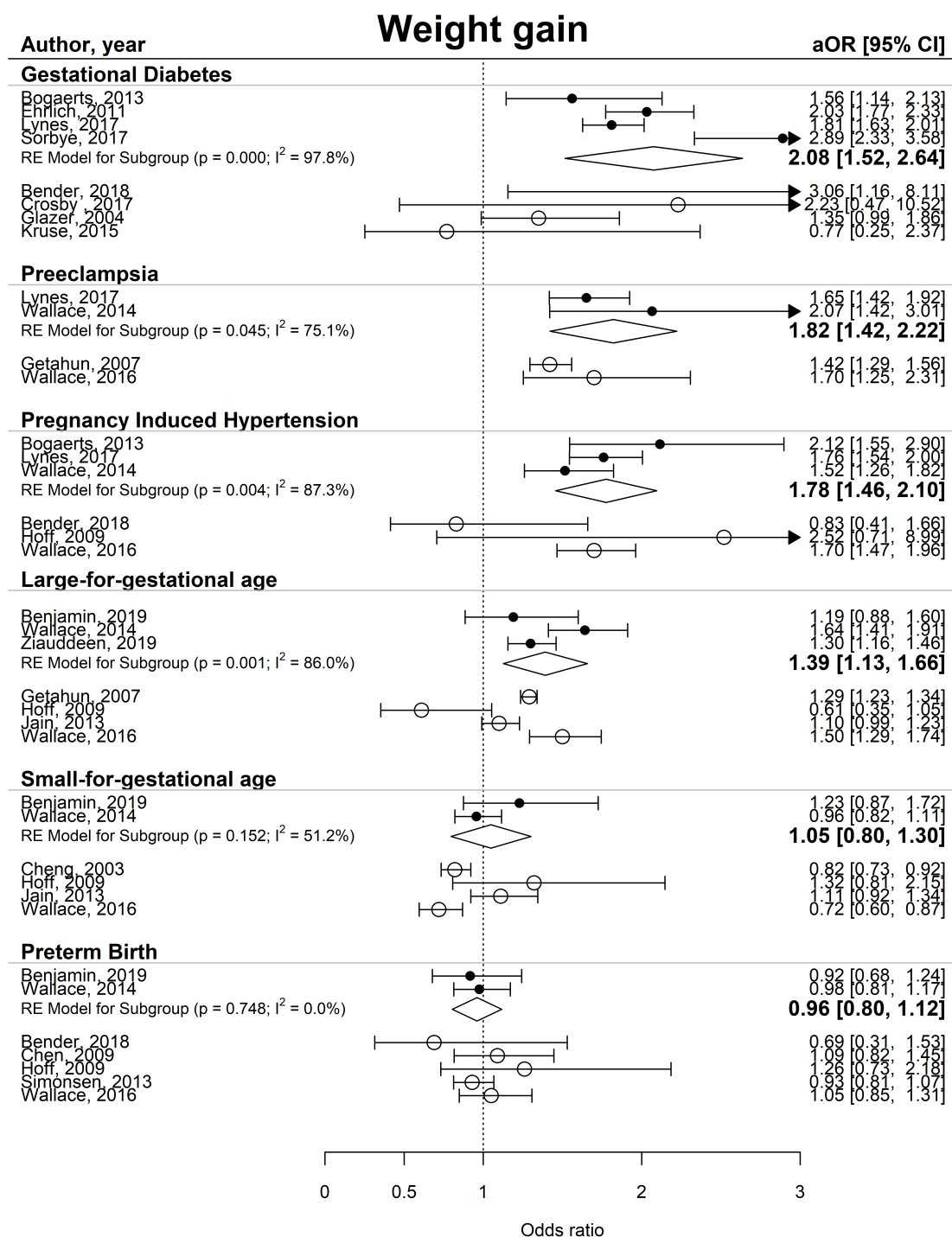


Fig. 2.7 Forest plot from random effects meta-analysis showing the crude odds ratios for the association between interpregnancy weight gain and the risk for perinatal outcomes of interest. Black, solid dots represent studies with reference group of interpregnancy weight change between -1 and +1 BMI unit and are therefore included in the meta-analyses. White, open dots represent studies not using a reference group of interpregnancy weight change between 1-unit weight loss and 1-unit weight gain and are visually displayed but not included in the meta-analysis. cOR, crude odds ratio; CI, confidence interval.

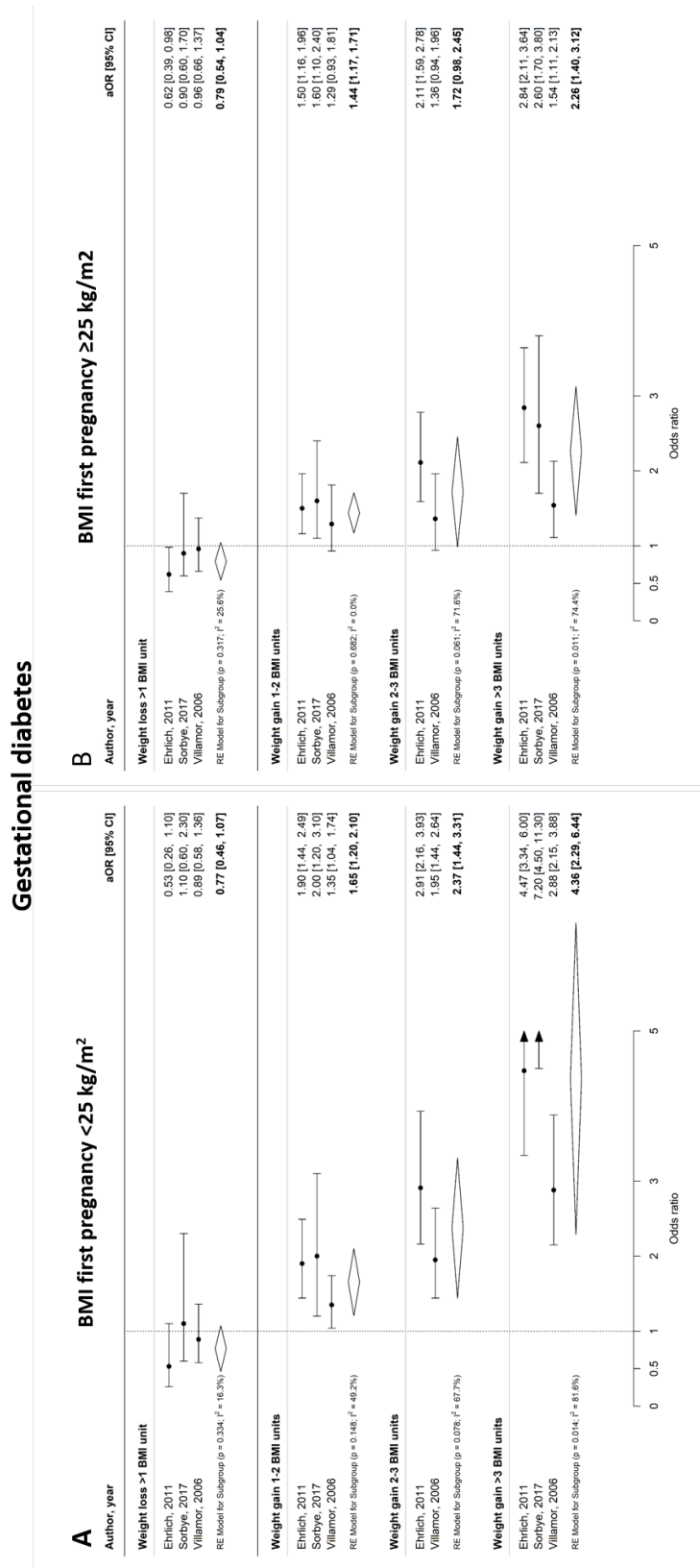


Fig. 2.8 Forest plot from random effects meta-analysis showing association between interpregnancy weight change and the risk of developing gestational diabetes, stratified by BMI category at the start of index pregnancy. A, Normal weight classified as BMI <25 kg/m²; B, Overweight classified as BMI ≥ 25 kg/m². All adjusted odds ratios are relative to the reference category of interpregnancy weight change between -1 and +1 BMI units. BMI, body mass index (in kg/m²); aOR, adjusted odds ratio; CI, confidence interval.

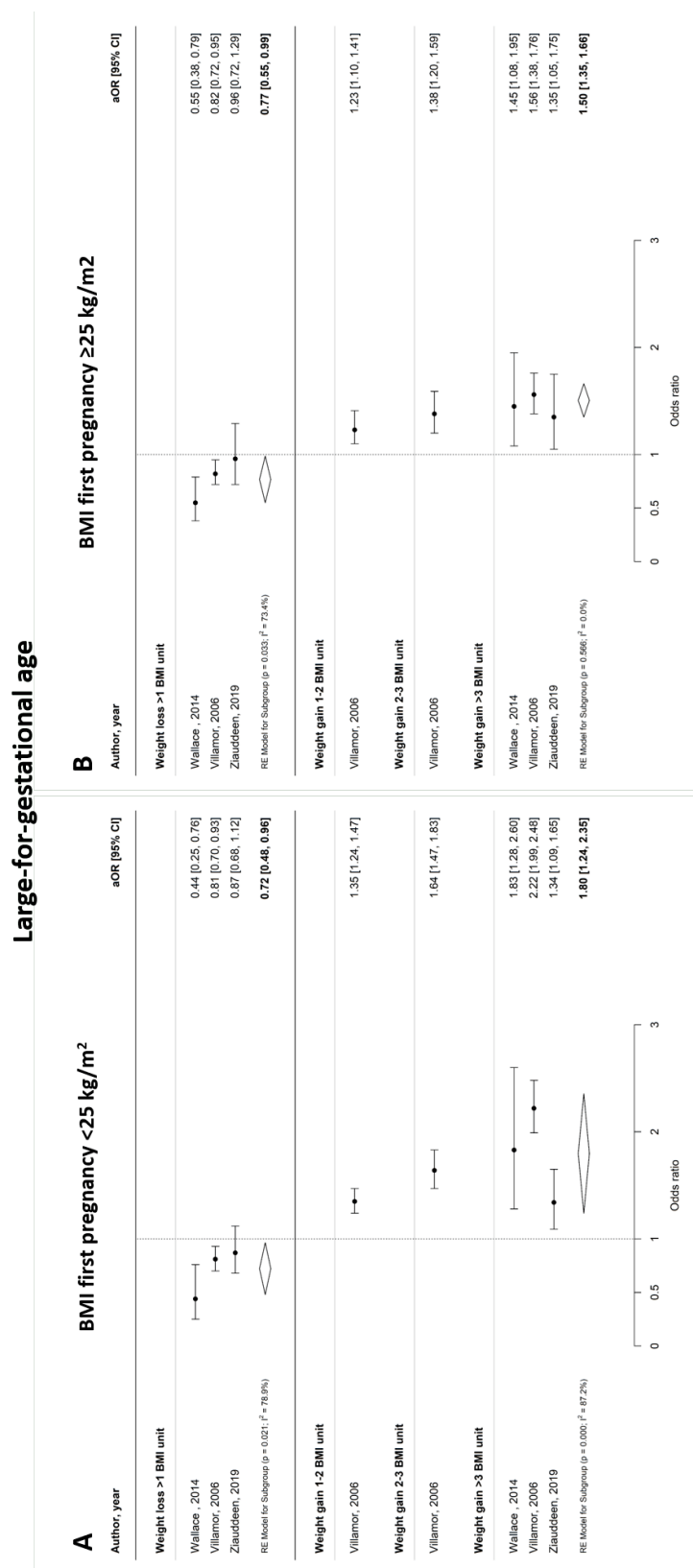


Fig. 2.9 Forest plot from random effects meta-analysis showing association between interpregnancy weight change and the risk of delivering a large for gestational age neonate, stratified by BMI category at the start of index pregnancy. A, Normal weight classified as BMI <25 kg/m²; B, Overweight classified as BMI ≥25 kg/m². All adjusted odds ratios are relative to the reference category of interpregnancy weight change between -1 and +1 BMI units. BMI, body mass index (in kg/m²); aOR, adjusted odds ratio; CI, confidence interval.

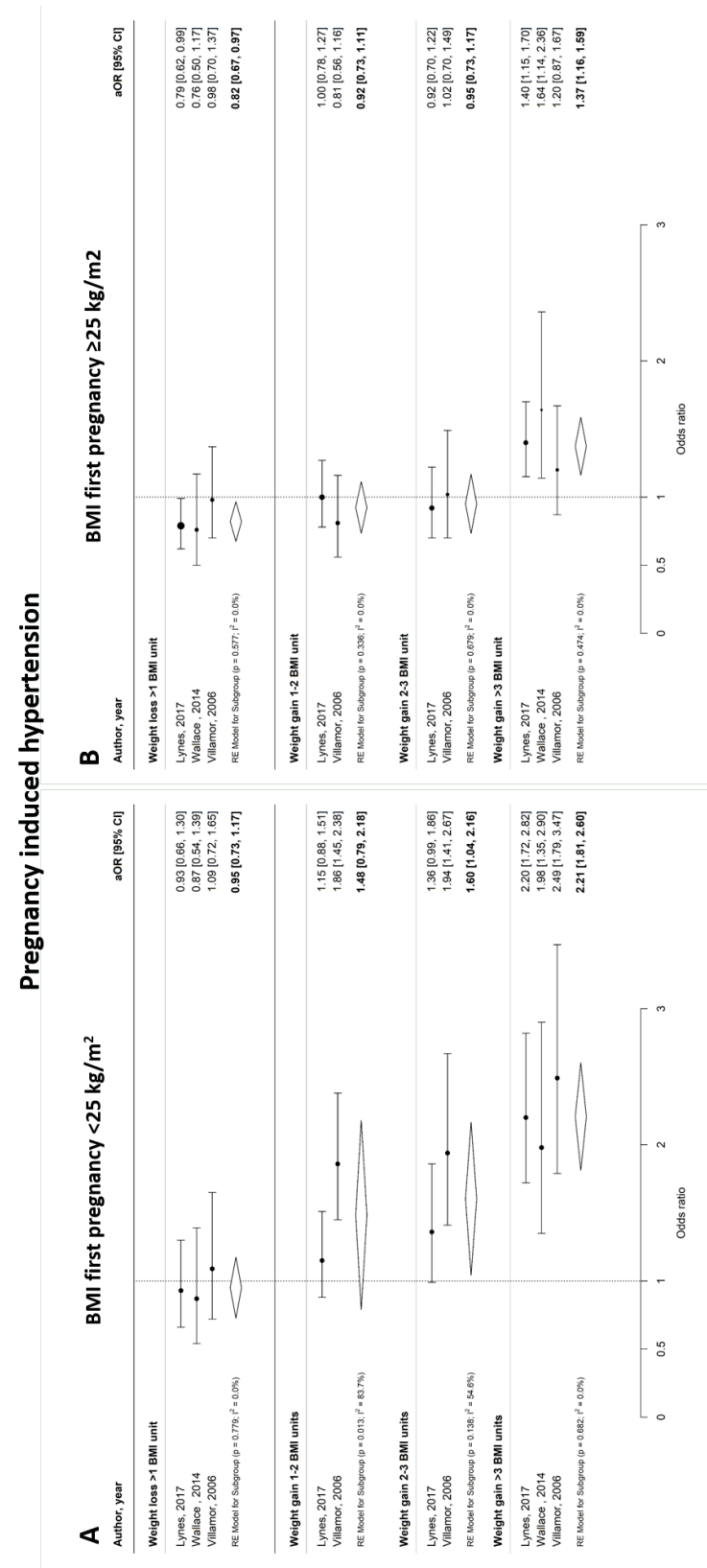


Fig. 2.10 Forest plot from random effects meta-analysis showing association between interpregnancy weight change and the risk of developing pregnancy induced hypertension, stratified by BMI category at the start of index pregnancy. A, Normal weight classified as BMI <25 kg/m²; B, Overweight classified as BMI ≥25 kg/m². All adjusted odds ratios are relative to the reference category of interpregnancy weight change between -1 and +1 BMI units. BMI, body mass index (in kg/m²); aOR, adjusted odds ratio; CI, confidence interval.

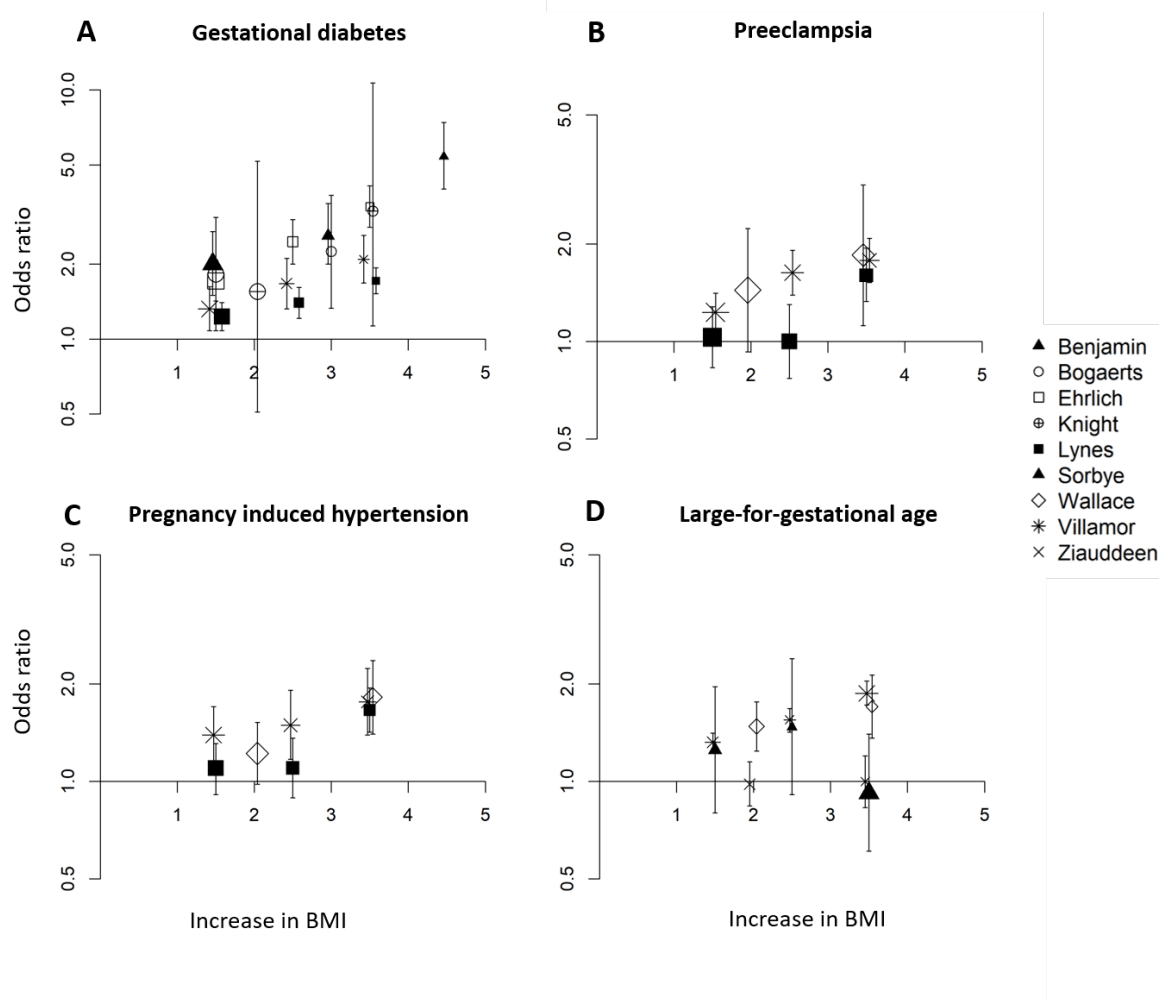


Fig. 2.11 Dose-response curve for the increase in odds ratio of developing perinatal complications after interpregnancy weight gain. A Gestational Diabetes. B preeclampsia. C Pregnancy Induced Hypertension D Large for gestational age. Where ranges of BMI changes were reported, the midpoint category was utilised (e.g. 1.5 BMI units change for the category weight change between 1 and 2 BMI units). aOR, adjusted odds ratio. BMI, body mass index (in kg/m^2).

Table 2.3 Assessment of study quality through the Newcastle-Ottawa Scale

	Bogaerts 2013	Bender 2019	Benjamin 2019	Chen 2009	Cheng 2003	Crosby 2017	Ehrlich 2011	Getahun 2007 (PE)	Getahun 2007 (LGA)	Glazer 2004	Hoff 2009	Jain 2013	Knight-Agarwal 2016	Kruse 2015	Lynes 2017	McBain 2016	Pole 1999	Simonsen 2013	Sorbye 2017	Villamor 2006	Wallace 2014	Wallace 2016	Ziauddeen 2019
Selection																							
1	*	*	*	*	*	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
2	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
3	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
4	-	-	-	*	*	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Comparability																							
5	*	-	-	*	*	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Outcome																							
6	-	*	-	*	-	-	*	*	*	-	*	*	*	*	*	*	*	*	*	*	*	*	*
7	*	*	*	*	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Total (out of 9)	5	5	3	7	5	3	8	7	6	4	5	6	5	6	5	5	5	3	6	5	5	9	9

Quality assessment of studies through the Newcastle–Ottawa scale addresses three different areas: selection criteria, comparability of cases and controls, and outcome assessment. Scores range from 0-9, where nine was considered of highest quality. A maximum score of nine stars could be allocated to each study: four for selection, two for comparability and three for outcome. Studies were assessed according to the cohort studies assessment criteria, with exception of * Cheng, which was assessed as a case-control study.

2.5 Discussion

2.5.1 Main findings

This study systematically summarises and examines the published literature on the associations between interpregnancy weight change and several common perinatal outcomes. Our main findings are that interpregnancy weight gain is associated with a higher risk of developing GDM, PE, PIH and delivering an LGA neonate, while interpregnancy weight loss is associated with a lower risk of delivering an LGA neonate. BMI at the start of the index pregnancy possibly modifies the risk of developing GDM, PIH or delivering an LGA neonate after interpregnancy weight gain. Furthermore, we identify an approximately positive log-linear relationship between interpregnancy weight gain and the risk of developing GDM, PE, PIH or delivering a LGA neonate.

2.5.2 Comparison with existing literature

Our study confirms the associations between interpregnancy weight gain and the risk of developing GDM and LGA, as also shown in a recent meta-analysis [254], despite the slight difference in reference groups. Furthermore, our research additionally summarises the effect of interpregnancy weight change on the risk of developing hypertensive disorders in pregnancy. Our meta-analysis is to the authors knowledge the first meta-analysis to show that gaining weight between pregnancies increases the risk of developing hypertensive disorders in the subsequent pregnancy. The observation that starting BMI possibly modifies this association is important for women with a healthy BMI at the start of their index pregnancy, as research often emphasises the risk associated with being overweight or obese, and women with a healthy BMI might not be aware of the risk that comes with (small) interpregnancy weight gain. Although the risks of (excessive) gestational weight gain [166] and high prepregnancy BMI [132, 255] on perinatal outcomes are well understood, the effects of interpregnancy weight gain are relatively unknown and are essential to understand in order to guide women in periconception and perinatal weight management.

Our study shows an approximate log-linear association between BMI gain and the risk of developing GDM or hypertensive disorders in pregnancy. This result contributes towards understanding the association between maternal weight and pregnancy complications. Linear dose-response associations are established between obesity and the incidence of GDM, PE and PIH [256], between adiposity and preeclampsia [257], as well as maternal weight and preeclampsia [132] and GDM [255]. Our identified associations emphasise the detrimental

effects of (small amounts of) weight gain, additional to the influence of absolute BMI. This can contribute towards understanding the importance of post-partum weight management and highlights the need for the development of clinical guidelines.

As many guidelines recommend prenatal weight loss for overweight and obese women, the postpartum period could be an optimal target for reducing postpartum weight retention and therefore possibly mitigate the higher risk of adverse perinatal outcomes in a subsequent pregnancy. A recent systematic review focusing on postnatal weight management in overweight and obese women showed that a dietary or physical activity intervention was associated with greater weight loss in the postpartum period than no intervention [191]. Two further meta-analyses focusing on women of all weight categories showed that diet-and-exercise interventions that use self-monitoring result in the greatest weight loss postpartum; the pooled weight loss was 2.3kg up to 36 months from baseline [258]. Importantly, diet and exercise together resulted in double the weight loss compared to an exercise intervention alone [259]. Further randomised trials are proposed and will be assessing feasibility and cost-effectiveness of access to a slimming group (SWAN trial) [260] and delivering an (evidence based) intervention via text messaging (intervention adaptation and SMS feasibility RCT) [261].

2.5.3 Strengths and limitations

A strength of our study is we ensured a homogeneous reference group (i.e. a BMI change $\leq 1\text{kg/m}^2$) for our meta-analysis rather than including studies with different reference groups [254]. Furthermore, we only harmonised studies reporting adjusted odds ratios, which all considered maternal age, country of origin, social economic status and smoking status as potential confounders.

Nevertheless, our study has several limitations. First, between-study heterogeneity remained, arising from differences in outcome definitions and demographics, such as parity and age, and potentially differences in length of interpregnancy intervals and prevalence of perinatal complications. Of the studies selected for meta-analysis, only Lynes et al. [182] did not restrict to nulliparous women, although removing this study had little impact on the results. Second, GDM, PE and PIH were either not defined in publications or the definitions of these adverse outcomes differed between studies, hence caution is needed when comparing effect estimates between studies. Third, it was not possible to consistently assess the impact of previous pregnancy complications, which may lead to excessive interpregnancy weight changes and a higher risk of subsequent pregnancy complications. Fourth, studies varied in

the way they measured prepregnancy weight, with the majority of studies using self-reported weight (and height) to calculate BMI and interpregnancy weight change. Although evidence suggests that maternal reports of prepregnancy weight are in general consistent with clinical records [262], bias due to systematic over- or under-reporting cannot be excluded. We can also not exclude the possibility of publication bias, as this could not be assessed due to the small number of studies available per adverse outcome and funnel plot assessment is generally not recommended with less than 10 studies [263]. Lastly, we were unable to make the distinction between spontaneous preterm birth and medically induced preterm birth. We hypothesise that an increased risk of preterm birth is at least partly related to the increased risk of carrying an SGA neonate, as (suspected) growth restriction is one of the main causes of medically induced premature birth [264]. However, inadequate nutrition in the context of severe maternal weight loss could also contribute to a higher risk of both SGA and preterm birth [265].

2.5.4 Conclusion

Our study highlights the importance of postpartum weight management, but also identifies opportunities for future research. Effective strategies for postpartum weight management are being elucidated, with future trials focusing on easy-access and cost-effectiveness of evidence based dietary- and exercise interventions. Furthermore, it will be particularly important to encourage postpartum weight loss in normal weight women, as this group might not be the focus of current research and interventions, yet may be at highest risk of adverse outcomes from interpregnancy weight gain.

In conclusion, we show that interpregnancy weight gain impacts on the risk of developing perinatal complications in a subsequent pregnancy and it is possible that BMI at the index pregnancy modifies these associations. These findings highlight the need to encourage women to return to their prepregnancy weight before conceiving again in an effort to reduce the risk of perinatal complications. Future work should focus on defining the most effective strategies to achieve this outcome.

Chapter 3

Description of the Pregnancy Outcome Prediction Study

3.1 Chapter summary

The aim of this chapter is to describe the data set used for the analyses in Chapters 4, 5 and 6. This is the Pregnancy Outcome Prediction (POP) study, conducted in the Rosie hospital in Cambridge, UK between January 2008 and July 2012.

The POP study is a prospective cohort study, phenotyping nulliparous women who were recruited at their dating scan (~12 weeks gestational age). They underwent serial research ultrasound scans, as well as phlebotomy measurements, across all three trimesters of pregnancy. This was performed in parallel with their normal perinatal care.

A unique characteristic of the POP study is that women and clinicians were blinded to the outcome of the research scans, thereby avoiding extra interventions based on participation in the study. This also facilitated an excellent opportunity to identify effective ultrasonic screening methods for common perinatal complications, such as fetal growth abnormalities. Furthermore, the longitudinal phlebotomy samples facilitated the identification of novel biomarkers for perinatal complications.

Most POP study publications so far, including the ones in this thesis, have focused on perinatal complications associated with placental dysfunction, e.g. preeclampsia and fetal growth restriction. Major findings of previous POP study publications include the identification of novel biomarkers 4-hydroxyglutamate for screening of preeclampsia, delta-like homologue-1 for identification of fetal growth restriction and the polyamine N1,N12-diacetylspermine for which opposite associations between these two conditions were shown for the first time. Furthermore, more evidence on the effectiveness of universal screening for fetal growth abnormalities was gathered. However, implementation of such screening depends on confirmation of effectiveness in randomised trials and availability of suitable interventions or treatments.

3.2 Background of the POP Study

3.2.1 Aims of the POP study

The POP study is a prospective cohort study which included unselected nulliparous women who attended the Rosie Hospital in Cambridge UK between 14th January 2008 and 31st July 2012 with a viable singleton pregnancy. The rationale behind the POP study was to provide a study design with the primary aim of generating clinically useful methods to screen women and assess their risk of adverse perinatal outcomes [266]. This aim was further split into (i) evaluating known biomarkers of serial ultrasonography assessments of fetal and maternal well-being, and (ii) identifying novel biomarkers [267].

The motivation of only including nulliparous women was that they have a higher absolute risk of perinatal complications compared to multiparous women, and lack information on previous pregnancy outcomes, which is indicated as one of the most important risk factors for adverse outcomes in subsequent pregnancies.

Routine antenatal care in the United Kingdom for women in their first pregnancy consists of 10 routine midwife visits [70], however, this intense schedule reflects a poor discrimination of risk, as most adverse perinatal outcomes occur in women who are deemed low-risk at their booking appointment. Furthermore, the primary screening methods implemented by the midwives is measurement of the symphyseal-fundal height, routine blood pressure checks and urine test for proteinuria [70], which tend to have low sensitivity for perinatal complications. The POP study was developed with the aim to contribute to the development of more personalised antenatal care, where frequency and timing of visits is proportionate to the individual risk, estimated by a combination of clinical records and biomarkers [267].

A unique characteristic and major strength of the POP study was that clinicians and patients were blinded to the ultrasound results, unless one of the following were detected: (i) major congenital abnormalities, (ii) placenta praevia, (iii) severe oligohydramnios or (iv) breech presentation at 36 weeks gestational age (wkGA).

3.2.2 Recruitment and research visits

A total of 8,028 women were eligible for inclusion in the POP study, and 4,512 (56%) gave informed consent for participation. Eligible but non-recruited women were younger, more often of non-white ethnicity, more likely to be current smokers, and more often delivered a

growth restricted neonate than eligible women who were recruited to the study [267]. Of the eligible and recruited women, 4,212 (93.4%) completed the study protocol. Sixty-seven participants withdrew consent over the course of the study and 223 women delivered elsewhere. A full study flow diagram can be found in Figure 3.1

Women were recruited when attending the Rosie hospital for their dating scan (~12 weeks gestational age [wkGA]), and after inclusion attended a further three research appointments 8 weeks apart (~20 wkGA, ~28 wkGA and ~36wkGA). Additionally, women followed the standard antenatal care for nulliparous women in the United Kingdom. Participating women had blood taken at all four research visits. On the visits at 20, 28 and 36 wkGA, research ultrasound scans were performed to assess fetal biometry and Doppler flow velocity in the umbilical and uterine arteries. At the 20 wkGA appointment, women were asked to fill out a questionnaire about their demographics and medical history. If a partner was present at the 20 wkGA research visit, a sample of their DNA was taken, and their height and weight measurements collected. The final research visit at 36 wkGA was intended to screen for complications that arise at term and for which early intervention can prevent worsening of the condition of mother and fetus.

Alongside the clinical data and the ultrasonic measurements used in this thesis, DNA samples from both parents, maternal bloods samples and placentae were collected. The maternal blood samples were taken on the same days as the research scans and immunoassays for potential markers of perinatal complications (e.g. Alpha Fetoprotein, Pregnancy Associated Plasma Protein A) were run. Although not used in the analysis in this thesis, the POP study extensively collected placentae for morphological assessment and of which a subset been biopsied and cut for microscopy. An overview of data collected in the POP study can be found in Figure 3.2

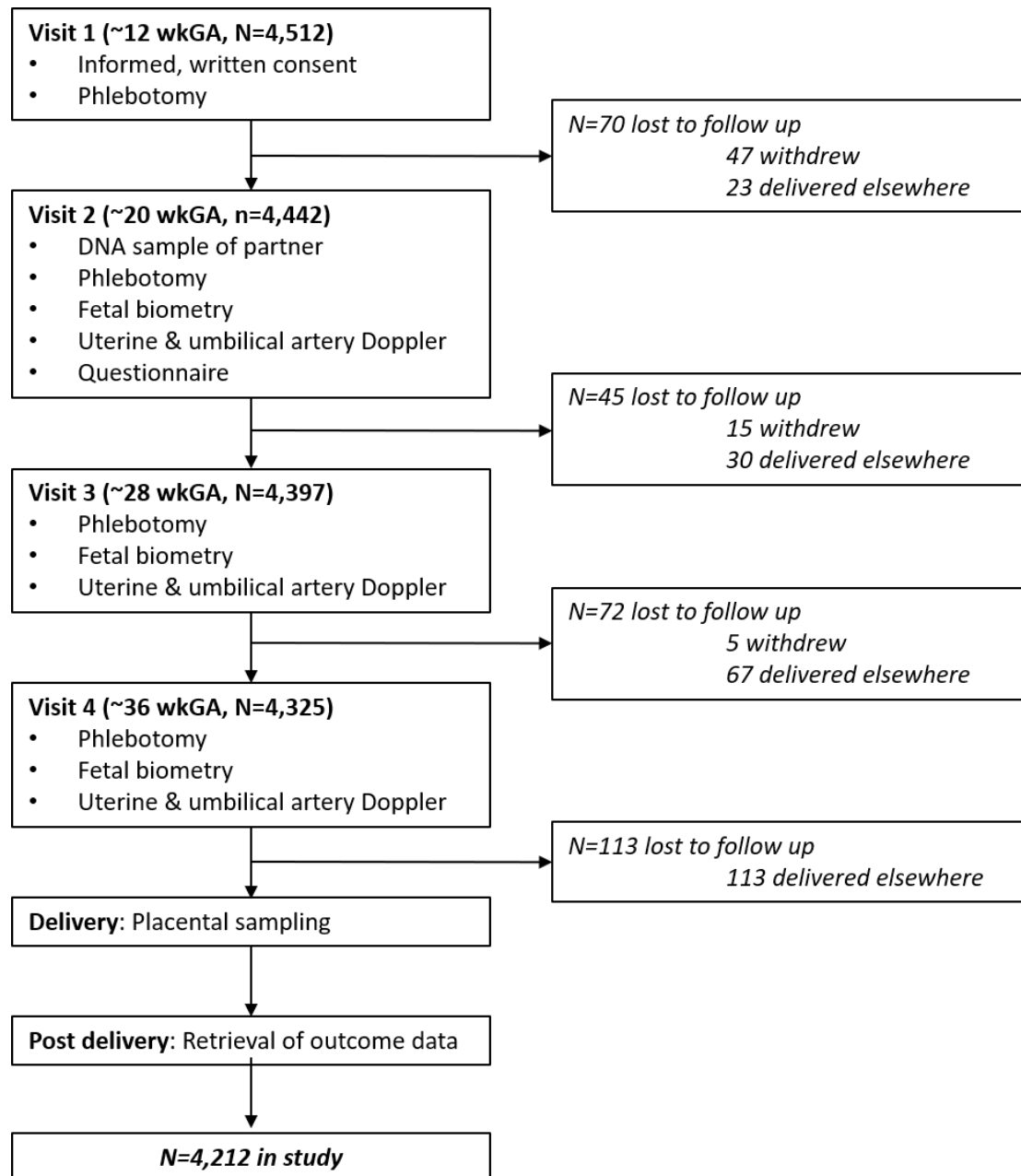


Fig. 3.1 Flow chart of the Pregnancy Outcome Prediction Study. Adapted from Gaccoli et al. 2017 [267]. WkGA; weeks gestational age

3.3 Definitions in the POP study relevant for this thesis

The definitions of outcomes, exposures, and covariates in the POP study relevant for this thesis are defined in Table 3.1 and described below.

3.3.1 Maternal weight

Maternal weight (in kg) was recorded for the first time at booking scan (~12 wkGA). The POP study did collect data on self-reported prepregnancy weight, but due to small numbers and low accuracy the 12 wkGA measurement was used in all analyses as a proxy for prepregnancy weight. Maternal weight was subsequently recorded at all other research visits. Body Mass Index (BMI) was calculated with the formula:

$$BMI(kg/m^2) = \frac{Weight(kg)}{Height(m)^2}$$

For further analyses in this thesis, BMI was classified according to the World Health Organisation BMI categories, where BMI <18.5 kg/m² is classified as underweight, 18.5-24.9 kg/m² as normal weight, 25.0-29.9 kg/m² as overweight and ≥30 kg/m² classified as obese [268]. As the group with underweight BMI was too small for inception (n=68), this group was merged with normal weight women. Seven participants (0.2%) had no information available on their prepregnancy BMI.

3.3.2 Maternal characteristics

Most of the maternal characteristics listed in Table 3.1 were collected via self-reporting questionnaire at the 20-week scan. This could not have been done earlier, as women were only recruited at their booking scan (~12 wkGA). Questions included maternal age, marital status, occupation and partners occupation, age at completing full time education, smoking status, alcohol units per week currently, current prescription medication, current medical conditions, previous miscarriages and use of contraceptive pill in the 3 months before conceiving. See Appendix 2 for the self-reporting questionnaire form.

3.3.3 Umbilical and uterine artery Doppler measurements

The pulsatility index of the uterine and umbilical arteries were recorded at ~20-, ~28- and ~36 wkGA. All sonographers undertaking uterine artery doppler measurements attended

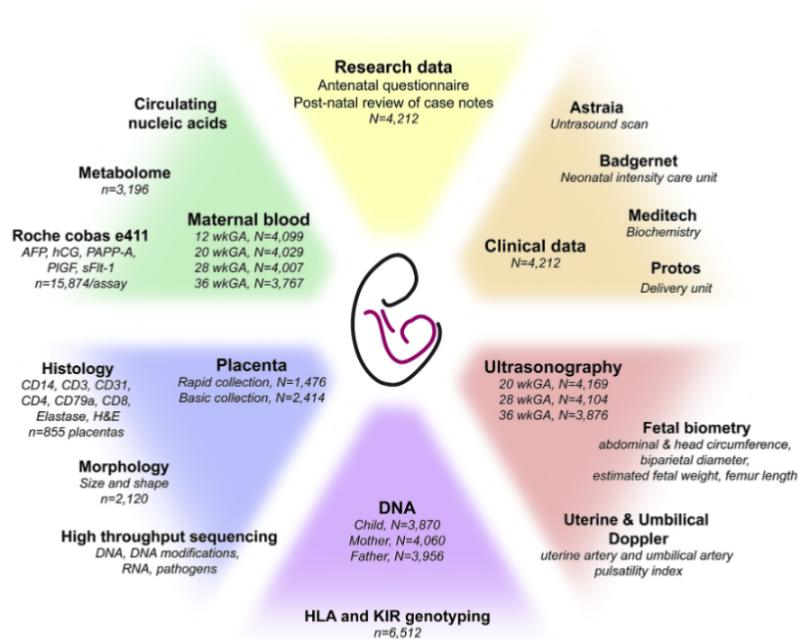


Fig. 3.2 Overview of data collected in the POP study. Adapted from Gaccoli et al. 2017 [267]

training sessions and were assessed as competent to perform uterine artery doppler by the head of the Rosie Ultrasound Department. The uterine artery measurements were taken on both the left and right side, and any notches were recorded. In the umbilical artery, the pulsatility index and the presence of end diastolic flow was recorded.

3.3.4 (Repeated) fetal growth measurements

Fetal biometry was assessed in the 20-, 28- and 36- week scan. Biparietal diameter, head circumference, abdominal circumference and Femur length were recorded. From these measurements, estimated fetal weight was calculated, using coefficients from the Gestation-Related Optimal Weight (GROW) calculator (version 6.7.3.13). Abdominal circumference growth velocity was calculated as the difference in abdominal circumference Z score, comparing the last scan before birth and the scan at 20 weeks [104].

Variable	Definition	Cases (%)	Missing (%)
Pregnancy characteristics			
Maternal age	Age at recruitment. Free text reporting.	NA	0 (0)
Maternal ethnicity	Self-reported via questionnaire at the 20 wkGA scan. Categories (self-identification): white, other	White: 3900 (92.6) Non-white: 240 (5.7)	72 (1.7)
Deprivation score	Index of Multiple Deprivation 2007 [269], based on census data from the area of the mother's postcode. Used as a proxy for socio-economic status. Divided into quartiles.	NA	172 (4.1)
Age stopped full time education	Self-reported via questionnaire at the 20 wkGA scan. Used as a proxy for socio-economic status. Free text reporting.	NA	126 (3.0)
Marital status	Self-reported via questionnaire at the 20 wkGA scan. Categories: Married, Cohabiting, Single. Used as a proxy for socio-economic status.	Married: 2863 (68.0) Other: 1349 (32.0)	0 (0)
Smoking status	Self-reported via questionnaire at the 20 wkGA scan. Categories: (0) never smoked, (1) quit before pregnancy, (2) quit during pregnancy, (3) current smoker.	Never smoked: 2503 (59.4) Quit before pregnancy: 1163 (27.6) Quit during pregnancy: 335 (8.0) Current smoker: 211 (5.0)	0 (0)
Pre-existing diabetes	Self-reported via questionnaire at the 20wkGA scan under 'current medical conditions'.	16 (0.4)	0 (0)
Pre-existing hypertension	Self-reported via questionnaire at the 20wkGA scan under 'current medical conditions'.	220 (5.2)	0 (0)
(Repeated) measurements during gestation			
Gestational age ^a	Estimated gestational age at time of scan, as recommended [70]	NA	20wkGA: 28 28wkGA: 102 36wkGA: 324 1 (<0.1) 7 (0.2)
(Prepregnancy) weight Body mass index	Weight (in kg), measured on the day of booking scan Calculated from maternal weight (in kg) and height (in m), both measured on day of booking scan. Categories based on WHO criteria: underweight (≤ 18.5 kg/m ²), normal weight (18.5-24.9 kg/m ²), overweight (25.0-29.9 kg/m ²) and obese (≥ 30 kg/m ²).	NA Normal weight: 2444 (58.1) Overweight: 1187 (28.2) Obese: 574 (13.7)	
Umbilical artery PI ^a	Quantified at the 20, 28- and 36-weeks scan as the mean PI of the left and right uterine arteries	NA	20wkGA: 70 28wkGA: 119 36wkGA: 353
Uterine artery PI ^a	Quantified at the 20, 28- and 36-weeks scan.	NA	20wkGA: 133 28wkGA: 193 36wkGA: 441
Abdominal circumference growth velocity	Difference in abdominal circumference Z score, comparing the last scan before birth and the scan at 20 wkGA. Categorised in deciles.	NA	347 (8.2)

Variable	Definition	Cases (%)	Missing (%)
Perinatal outcomes			
Gestational diabetes	During the first two years of the study (2008-2010), gestational diabetes diagnosis was based on the World Health Organisation recommendations (1999). From 2011 onwards, the International Association of Diabetes and Pregnancy Study recommendations were used for the diagnosis of gestational diabetes [270]	191 (4.5)	6 (0.1)
Preeclampsia	New onset of hypertension after 20 weeks of gestation, with proteinuria or systemic findings as mentioned in the ACOG 2013 classification [51]	273 (6.5)	5 (0.1)
Gestational hypertension	New onset of hypertension after 20 wkGA, without proteinuria or systemic findings as mentioned in the ACOG 2013 classification [51]	85 (2.0)	5 (0.1)
Small for gestational age	Sex- and gestational age-specific birth weight percentile <10 th	372 (8.8)	31 (0.7)
Large for gestational age	Sex- and gestational age-specific birth weight percentile >90 th	197 (4.7)	31 (0.7)
Spontaneous preterm birth	Birth <37 wkGA in absence of induction	113 (2.7)	41 (1.0)
Livebirth	All live births ≥24 weeks, based on (i) Postnatal hospital database (ii) delivery database Protos and (iii) neonatal intensive care database Badgernet	4161 (98.8)	3 (0.1)

Table 3.1 Overview of the most used definitions in this thesis, for data collected in the POP study. BMI; Body Mass Index, PI; pulsatility index, wkGA; weeks gestational age. ^aMissing values represent 20-, 28- and 36wkGA scan missing values, respectively.

	Normal weight (n=2444)	Overweight (n= 1187)	Obese (n= 574)	p-value	Total cohort* (n=4212)
Baseline characteristics					
Gestational age at booking scan (w)	12.6 (0.8)	12.6 (0.8)	12.6 (0.9)	0.51	12.6 (0.9)
Maternal age (y)	29.9 (4.8)	30.4 (5.3)	29.3 (5.7)	<0.001	30.0 (5.1)
Maternal weight at booking scan (kg)	60.5 (6.6)	73.5 (6.7)	92.3 (12.7)	<0.001	68.5 (13.5)
Maternal height (cm)	165.6 (6.5)	164.7 (6.4)	164.4 (6.2)	<0.001	165.2 (6.4)
Systolic BP at booking scan (mmHg)	106.4 (11.2)	109.5 (11.0)	114.5 (11.3)	<0.001	108.4 (11.5)
Maternal ethnicity				0.02	
White	2239 (91.6)	1111 (93.6)	544 (94.8)		3900 (92.6)
Non-white	158 (6.5)	58 (4.9)	23 (4.0)		240 (5.7)
Unknown	47 (1.9)	18 (1.5)	7 (1.2)		72 (1.7)
Marital status				<0.001	
Married	1713 (70.1)	798 (67.2)	346 (60.3)		2863 (68.0)
Not married	731 (30.0)	389 (32.8)	228 (39.7)		1349 (32.0)
Smoking status				<0.001	
Non-smoker	1547 (63.3)	658 (55.4)	292 (50.9)		2503 (59.4)
Quit pre-pregnancy	613 (25.1)	371 (31.3)	178 (31.0)		1163 (27.6)
Quit during pregnancy	166 (6.8)	106 (8.9)	63 (11.0)		335 (8.0)
Current smokers	118 (4.8)	52 (4.4)	41 (7.1)		211 (5.0)
Deprivation score				0.09	
1 (lowest)	595 (24.3)	301 (25.4)	121 (21.1)		1018 (24.2)
2	571 (23.4)	293 (24.7)	135 (23.5)		1002 (23.8)
3	589 (24.1)	289 (24.3)	138 (24.0)		1018 (24.2)
4 (highest)	593 (24.3)	250 (21.1)	158 (27.5)		1002 (23.8)
Unknown	96 (3.9)	54 (4.5)	22 (3.8)		172 (4.1)
Pre-existing diabetes	4 (0.2)	10 (0.8)	2 (0.3)	0.008	16 (0.4)
Pre-existing hypertension	69 (2.8)	76 (6.4)	75 (13.1)	<0.001	220 (5.2)
Perinatal outcomes					
Fetal sex				0.86	
Male	1225 (50.1)	596 (50.2)	294 (51.2)		2118 (50.3)

	Normal weight (n=2444)	Overweight (n= 1187)	Obese (n= 574)	p-value	Total cohort* (n=4212)
Female	1217 (49.8)	583 (49.1)	278 (48.4)		2080 (49.4)
Unknown	2 (0.1)	8 (0.7)	2 (0.3)		14 (0.3)
Gestational weight gain*					
12-20w	3.4 (2.2)	3.3 (2.6)	2.6 (2.5)	<0.001	3.2 (2.4)
20-28w	4.6 (2.3)	4.9 (2.2)	4.0 (2.3)	<0.001	4.6 (2.3)
28-36w	4.3 (2.2)	4.6 (2.4)	4.2 (2.7)	<0.001	4.3 (2.3)
12-36w	12.3 (3.7)	12.7 (4.4)	10.8 (5.5)	<0.001	12.2 (4.2)
Gestational diabetes				<0.001	
Yes	62 (2.5)	68 (5.7)	60 (10.5)		191 (4.5)
No	2380 (97.4)	1115 (93.9)	514 (89.5)		4015 (95.3)
Unknown	2 (0.1)	4 (0.3)	0 (0.0)		6 (0.1)
Preeclampsia				<0.001	
Yes	99 (4.1)	84 (7.1)	90 (15.7)		273 (6.5)
No	2342 (95.8)	1101 (92.8)	484 (84.3)		3934 (93.4)
Unknown	3 (0.1)	2 (0.2)	0 (0.0)		5 (0.1)
Gestational hypertension				<0.001	
Yes	31 (1.3)	30 (2.5)	24 (4.2)		85 (2.0)
No	2410 (98.6)	1155 (97.3)	550 (95.8)		4122 (97.9)
Unknown	3 (0.1)	2 (0.2)	0 (0.0)		5 (0.1)
Spontaneous preterm birth				0.42	
Yes	64 (2.6)	37 (3.1)	12 (2.1)		113 (2.7)
No	2366 (96.8)	1134 (95.5)	557 (97.0)		4058 (96.3)
Unknown	14 (0.6)	16 (1.3)	5 (0.9)		41 (1.0)
Small for gestational age				0.05	
Yes	239 (9.8)	90 (7.6)	43 (7.5)		372 (8.8)
No	2196 (89.9)	1084 (91.3)	528 (92.0)		3809 (90.4)
Unknown	9 (0.4)	13 (1.1)	3 (0.2)		31 (0.7)
Large for gestational age				<0.001	
Yes	95 (3.9)	51 (4.3)	51 (8.9)		197 (4.7)
No	2340 (95.7)	1123 (94.6)	520 (90.6)		3984 (94.6)

	Normal weight (n=2444)	Overweight (n= 1187)	Obese (n= 574)	p-value	Total cohort* (n=4212)
Unknown	9 (0.4)	13 (1.1)	3 (0.2)		31 (0.7)
Uterine artery PI >95 th centile at 20wkGA				0.66	
Yes	122 (5.0)	58 (4.9)	23 (4.0)		203 (4.8)
No	2266 (92.7)	1084 (91.3)	525 (91.5)		3876 (92.0)
Unknown	56 (2.3)	45 (3.8)	26 (4.5)		133 (3.2)
Umbilical artery PI >95 th centile at 36wkGA				0.87	
Yes	105 (4.3)	50 (4.2)	27 (4.7)		182 (4.3)
No	2160 (88.4)	1021 (86.0)	495 (86.2)		3677 (87.3)
Unknown	179 (3.2)	116 (1.3)	52 (9.1)		353 (8.4)
Birthweight ⁺ (g)	3368 (513)	3430 (548)	3485 (571)	<0.001	3401 (534)
Placental weight [#] (g)	451 (96)	470 (108)	489 (111)	<0.001	461 (103)

Table 3.2 Baseline and birth characteristics in the Pregnancy Outcome Prediction Study. Data are presented as mean (SD) or number (%). Difference in characteristics were tested using chi-squared and Kruskal-Wallis tests, as appropriate. *Seven women had missing information on BMI. *Gestational weight gain was available for 2409 women with normal weight, 1167 with overweight and 563 obese women between 12-20 weeks gestational age; for 2343 women with normal weight, 1130 with overweight and 549 obese women between 20-28 weeks gestational age; and for 2226 women with normal weight, 1055 with overweight and 511 obese women between 28-36 weeks gestational age. ⁺Birthweight was available for 2437 women with normal weight, 11176 with overweight and 571 obese women, [#]Placental weight was available for 2243 women with normal weight, 1090 women who are overweight and 514 women who are obese. BP; blood pressure, PI; Pulsatility index, wkGA; weeks gestational age.

3.4 Baseline and birth characteristics in the POP Study

The most relevant baseline and birth characteristics for this thesis from women participating in the POPS cohort, stratified by maternal BMI category, are described in Table 3.2. Overweight and obese women had a higher systolic blood pressure at booking scan than normal weight women. Furthermore, they tended to be more often of white ethnicity, not married and were more likely to be current smokers. Overweight and obese women more often suffered from pre-existing condition such as diabetes and essential hypertension than normal weight

women and were also more likely to develop perinatal complications (gestational diabetes, gestational hypertension, and preeclampsia). Additionally, overweight and obese women delivered larger babies than normal weight women, which is reflected in a higher mean birthweight and a higher incidence of large for gestational age births.

3.5 Review of the published literature of the POP Study

As mentioned in section 3.1, the main aim of the POP study was to identify clinically useful methods to screen women for adverse perinatal outcomes, by ultrasound assessment as well as scrutinising known and identifying novel (ratios of) biomarkers. The main outcomes of interest in the published POP study literature have been the risk of preeclampsia and/or fetal growth restriction. In this section I discuss the published POP study literature relevant for this thesis.

3.5.1 Maternal weight dynamics

No previous study in the POP cohort focused on the consequences of maternal obesity or gestational weight gain on perinatal outcomes. However, many analyses in the POP cohort reported on outcomes for which maternal obesity is a (major) risk factor, hence some relevant lessons can be learned from these related studies. Firstly, although National Institute for Health and Care Excellence (NICE) guidelines in the UK only consider women with a BMI ≥ 35 at moderate risk for preeclampsia, a simple risk prediction score based on the ASPRE trial model reveals that BMI along the whole spectrum is associated with an increased risk of preeclampsia [271].

Furthermore, maternal obesity was found to be negatively associated with placental efficiency. Salavati and colleagues concluded that, in the POPS cohort, maternal obesity was associated with a decreased birthweight-to-placental weight ratio (Figure 3.3) [272]. This ratio is often used to describe adequate placental nutrient supply, and a small ratio (i.e. a relatively large placenta) is associated with an increased risk of delivering a small for gestational age (SGA) neonate, suggesting that obese women have a less efficient placenta which in turn could lead to an increased risk of delivering an SGA neonate. The association between maternal obesity and the risk of delivering a small baby will be further investigated in **Chapter 6**.

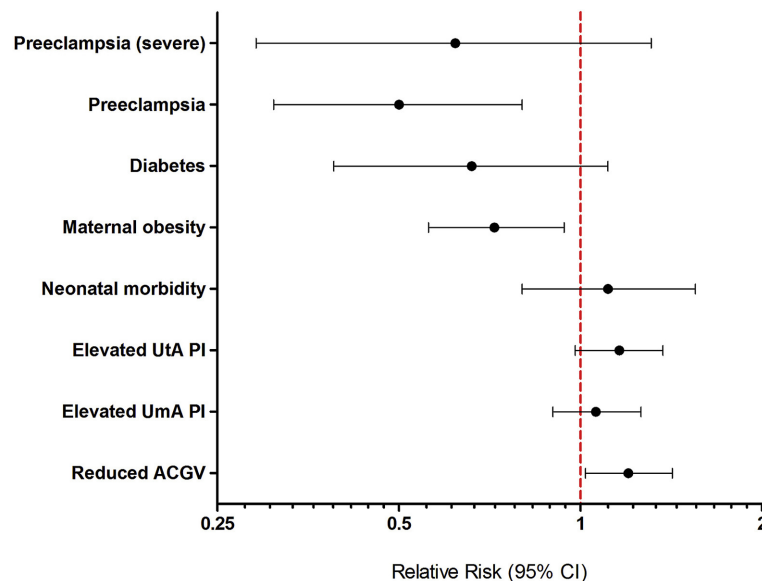


Fig. 3.3 Relative risks for low birth weight to placenta weight-ratio (Quintile 1 vs. Q2-Q4). Adapted from Salavati et al. 2018 [273]

3.5.2 Preeclampsia

As mentioned in **Chapter 1**, there are several well established biochemical (risk) factors related to preeclampsia. Due to the POP study being a prospective study on nulliparous women, without a previous history of preeclampsia, it provides an ideal opportunity to confirm and/or develop new screening markers for this complication.

Both soluble fms-like tyrosine kinase 1 (sFlt1) and placental growth factor (PlGF) are recognised biochemical markers for preeclampsia; an increased sFlt1 and a decreased PlGF are positively associated with preeclampsia. Sovio and colleagues tested the screening performance of a ratio of these two markers and divided the screening potential by low- or high-risk women based on the NICE guidelines [51, 274]. Women with a BMI >35 in the POP study, will fall in NICE's high risk category, as they are all nulliparous as well [70]. At 28 wkGA, this ratio has a positive predictive value (PPV) of 30.8% for preeclampsia with preterm delivery in high risk women, similar to the PPV for low-risk women. However, at 36 wkGA the score performs better for high risk compared to low-risk women (PPV of 20.3% vs 6.4% respectively) in predicting preeclampsia with severe features [274].

Furthermore, the metabolite 4-hydroxyglutamate was identified within the POPS cohort as a novel biomarker for preeclampsia and further validated in the Born in Bradford cohort. 4-Hydroxyglutamate was particularly predictive for preterm preeclampsia (<37 weeks delivery)

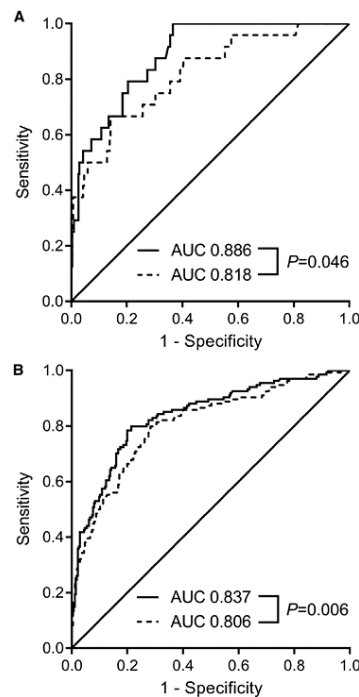


Fig. 3.4 Receiver operating characteristic curve analysis of the sFlt-1:PIGF ratio and 4-hydroxyglutamate in relation to pre-term and term pre-eclampsia. The ROC curve for (A) addition of 4-hydroxyglutamate to sFlt-1:PIGF ratio at 28 wkGA and pre-term pre-eclampsia and (B) addition of 4-hydroxyglutamate to sFlt-1:PIGF ratio at 36 wkGA and term pre-eclampsia. Dashed lines represent the sFlt-1:PIGF ratio measurements on their own and solid lines represent the models that include both sFlt-1:PIGF ratio and 4-hydroxyglutamate. AUC; Area under the curve, PIGF; Placental growth factor, sFLT; Soluble fms-like tyrosine kinase 1. Adapted from Sovio et al. [79]

at both 12, 20 and 28 wkGA [79] (Figure 3.4). Although maternal prepregnancy BMI is thought to be a stronger risk factor for preterm than term preeclampsia, the findings in this case-control study were independent of maternal (baseline) characteristics.

3.5.3 Fetal growth restriction

As fetal growth restriction is a major determinant of adverse perinatal outcomes, screening methods for effectively identifying fetuses at risk is of high priority. Due to the blinded nature of the POP study, it is very suitable for testing and developing adequate screening methods, both biochemically as well as ultrasonically.

In one of the first published studies from the POPS cohort, the effectiveness of universal versus selective ultrasound screening for the detection of SGA neonates was examined.

The study showed that, while selective ultrasonography detected one in five infants with birthweight <10th centile, universal screening at 28 and 36 wkGA tripled the detection of SGA neonates [104]. However, this was at a cost of reduced specificity (98% for selective and 90% for universal screening). No distinction was made in the screening effectiveness in normal weight or obese women, although it is known that ultrasonic fetal (biometry) measurements are less sensitive in obese women [275, 276].

Delta-like homolog 1 (DLK1) has been previously identified to shift nutrient metabolism towards fatty acid oxidation. However, for the first time, it was shown within the POP cohort that there is an association between DLK1 levels and the risk of delivering an SGA neonate. Additionally, this analysis split SGA neonates further in pathologically small and constitutionally small neonates and found that mothers carrying a pathologically small neonate had lower levels of circulating DLK1, while this association was not significant for women carrying a constitutionally small neonate [277]. Although not the focus of this study, it would have been of great interest to perform a sub-analysis to investigate whether this association holds up for women in different BMI categories.

As the sFlt1:PIGF ratio (described in **section 3.5.2** for the detection of preeclampsia) is thought to reflect a degree of placental insufficiency, the association between this ratio and an ultrasonically suspected SGA neonate was tested in the POPS cohort at both 28 and 36 wkGA. This revealed that the combination of an ultrasonically suspected SGA neonate with an elevated sFlt1:PIGF ratio (>85th centile) could identify a proportion of women at a higher absolute risk of adverse outcomes [278]. The definition for fetal growth restriction (FGR) as per Delphi panel procedure, that will be used for the analyses in **Chapter 6**, had a much lower positive predictive value for preterm delivery of an SGA neonate or term delivery of an SGA neonate plus an adverse outcome [278].

Although the sFlt1:PIGF ratio adds predictive value to ultrasonic screening alone, a further metabolite ratio predictive of term FGR was identified and validated in the POP cohort. The ratio between two strongly positive associated metabolites (1-(1-enyl-stearoyl)-2-oleoyl-GPC (P-18:0/18:1) and 1,5-anhydroglucitol) and two negatively correlated metabolites (5 α -androstan-3 α ,17 α -diol disulfate and N1,N12-diacetylspermine) had roughly double the discrimination capacity for term FGR, compared to the sFlt1:PIGF ratio (AUC 0.78 versus 0.64 respectively) [279]. Additionally, this ratio worked similarly irrespective of maternal BMI.

3.5.4 Concurrent mechanisms between preeclampsia & fetal growth restriction

As pregnancy-associated plasma protein A (PAPP-A) and alpha fetoprotein (AFP) are both associated with placentally-related adverse outcomes, and as they are often routinely measured during pregnancy for the risk prediction of fetal aneuploidy, a simple ratio between the two markers was tested for its predictive value for preeclampsia, FGR and stillbirth. A cut off for the ratio >10 was found to be associated with all these outcomes, without requiring correction for maternal characteristics such as weight [280]. The AUC of the uncorrected models varied from 0.674 for FGR, 0.651 for severe SGA and 0.716 for the combination of preeclampsia and delivering an SGA neonate.

Similarly, the cortisol-to-cortisone ratio was tested for its association with both preeclampsia and FGR, as it is hypothesised to reflect placental function. Both these conditions have previously been shown to be associated with reduced levels of 11- β -Hydroxysteroid dehydrogenase type 2, therefore it can be hypothesised that an increased cortisol-to-cortisone ratio could be predictive of both diseases. However, the opposite association was found in the POP cohort; there was a negative association between the cortisol-to-cortisone ratio and the risk of preterm and term preeclampsia, as well as preterm FGR [275] (Figure 3.5). No association with term FGR was found. As circulating cortisol levels are shown to be lower in (severe) obese pregnancies [281], it would be of great interest to see if this association is similar for normal weight and obese women.

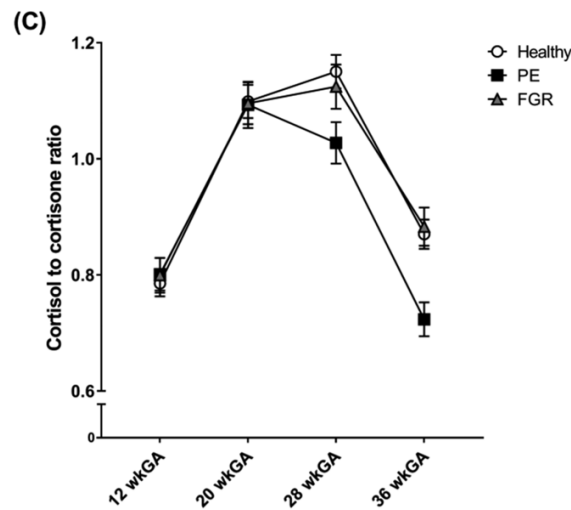


Fig. 3.5 Cortisol-to-cortisone ratio at 12, 20, 28, and 36 wkGA in healthy pregnancies, women that developed preeclampsia, and women who delivered a growth restricted infant. FGR; fetal growth restriction, PE; preeclampsia, wkGA; weeks gestational age. Adapted from Jayasuriya et al. 2019 [275]

3.5.5 Divergent mechanisms between preeclampsia & fetal growth restriction

Although preeclampsia and fetal growth restriction share a common background in placental dysfunction, the mechanisms leading to these conditions are not fully understood. It is unknown why placental dysfunction can lead to preeclampsia without fetal growth restriction and vice versa. An analysis of the placental methylome, transcriptome and maternal serum metabolome aiming to elucidate this showed that the maternal serum metabolite N1,N12-diacetylspermine had opposite associations with preeclampsia and fetal growth restriction. When classified in quintiles, having N1,N12-diacetylspermine levels in the highest quintile lead to a ~5-fold higher risk of developing preeclampsia compared to the lowest quintile, whereas N1,N12-diacetylspermine levels in the lowest quintile lead to a ~5-fold lower risk of FGR compared to the highest quintile [282] (Figure 3.6). However, the number of pregnancies affected by both conditions simultaneously was too small to elucidate this relationship further. Nevertheless, this is the first biomarker to show opposite associations between these two conditions and could be a key finding in untangling the pathways leading to preeclampsia or fetal growth restriction.

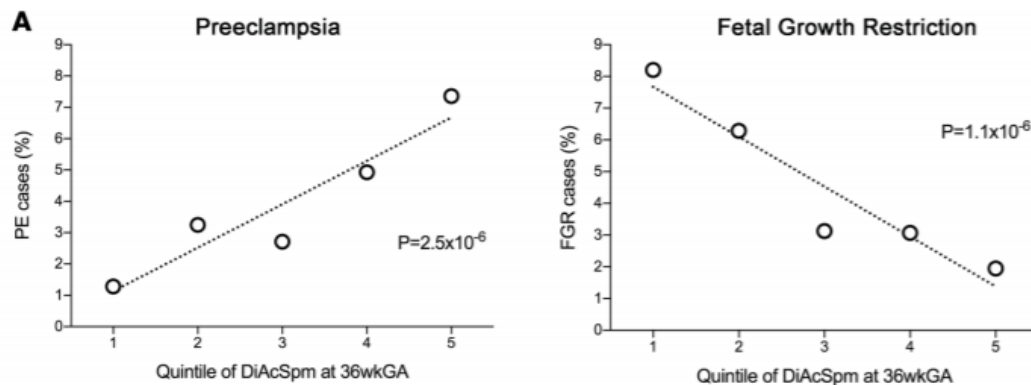


Fig. 3.6 Maternal serum levels of DiAcSpm by pregnancy complications. Adapted from Gong et al. 2018 [282]

3.6 Strengths and Limitations of the POPS cohort

The main strength of the POP study is that clinicians and patients were blinded to the results of the research scans and phlebotomy measurements. If results of these tests had not been concealed, they could have biased assessment and clinical treatment based on these research findings. Further justification of the concealment was that NICE does not recommend these universal scans to be offered routinely [70]. Naturally, women still had their regular perinatal care parallel to the POP study research scans.

Furthermore, another strength is that the serial research scans and phlebotomy measurement span all three trimesters of pregnancy. Ideally, data would also be available on maternal measurements and lifestyle before pregnancy, but this was unfeasible as this (i) would involve recruiting a large number of women and many of them might not follow through with a pregnancy in the time allocated for the study and (ii) information on prepregnancy health and subsequent health was out of the scope of the POP study.

A limitation of the POP study is that only nulliparous women were included in recruitment. Although there were valid reasons to do so (e.g. to limit complications of modelling with history of perinatal complications, as well as non-independence if women have more than one pregnancy in the study period [266]), nulliparous women have a higher rate of perinatal complications compared to multiparous women [283, 284]. Conclusions drawn from POP study analysis can therefore not be generalised to a multiparous population. However, as women included in the POPS study have no information available on previous perinatal

complications, a large proportion of them will be classified as ‘low-risk’, and there is an urgent need for improved risk prediction in this population.

Although the POPS cohort is a largely white and affluent population, this does not necessarily have to be a limitation. Due to the relative homogeneous characteristics of this population (e.g. nulliparous, white), we might be able to pick up a relatively ‘clear’ signal in analyses that is less diluted or interrupted by confounders. The signals picked up in a homogeneous population, like the POPS, can then be tested on further populations, to confirm associations in a wider population. A few POP study publications have validated their findings in the Born in Bradford cohort, a multi-ethnic and less affluent cohort.

3.7 Clinical implications of findings in the POPS cohort

Although studies in the POP cohort have identified and strengthened screening performance for preeclampsia and fetal growth restriction, none of the identified markers have yet been adopted into regular antenatal care. Low-cost, automated and relatively simple analyses platforms might not be available across all healthcare facilities and will differ between biomarkers. Furthermore, screening is only defensible if there is a suitable intervention or treatment available to mitigate the risk. For both preeclampsia and fetal growth restriction, the only intervention possible to date is to induce labour. This is more safely and easily performed near term. However, a balance needs to be struck between potential damage from iatrogenic (late) preterm birth and benefits of early intervention.

Randomised trials will have to be conducted to evaluate the effectiveness and outcomes of screening for preeclampsia and/or growth restriction. A previous randomised trial has shown an improved outcome after immediate induction of labour in women with preeclampsia near term [285], but limited data are available on earlier interventions. To further understand the benefits and disadvantages of interventions in women that screen as high risk, the POP 2 study started recruiting participants in early 2020. The aim of this observational study is to collect more data from new nulliparous women to investigate effective screening methods. Additionally, screening results will be revealed at 36 weeks and women will be asked to participate in a randomised trial for early labour induction when screened high risk for perinatal complications.

3.8 Conclusion

The POP study has generated a large dataset, with thorough phenotyping throughout. To date, the published literature from the POP cohort has mainly focussed on developing effective screening methods for placentally related perinatal complications. However, randomised trials will have to establish the clinical benefits of screening versus harm caused by (early) intervention before implementation into clinical practice.

In this thesis, I will leverage the extensive POP dataset to investigate the relationship between maternal weight dynamics and ultrasonic measurements of adaptation to pregnancy (**Chapter 4**) and placentally related complications (**Chapter 5 and 6**) with the aim of advising perinatal care for overweight and obese women. Further definitions, strengths and limitations for these analyses will be separately discussed in their respective chapters.

Chapter 4

Independent influences of maternal obesity and fetal sex on maternal cardiovascular adaptation to pregnancy

This chapter has been published in the International Journal of Obesity, including text and all figures. Contributions for each author can be found in the Acknowledgement section of this thesis.

Teulings NEWD, Wood AM, Sovio U, Ozanne SE, Smith GC, Aiken CE. Independent influences of maternal obesity and fetal sex on maternal cardiovascular adaptation to pregnancy: a prospective cohort study. International Journal of Obesity. 2020 Jun 15:1-0.

4.1 Chapter summary

Background: Successful pregnancy requires creation of low resistance utero-placental and feto-placental circulations and incomplete remodelling of this vasculature can lead to maternal or fetal compromise. Maternal BMI and fetal sex are known to influence vascular compliance and placental development, but it is unknown if these are independent or synergistic effects. Here we aim to investigate the impact of maternal obesity, fetal sex, and any interaction thereof on maternal cardiovascular adaptation to pregnancy, by assessing the physiological drop of uterine artery doppler pulsatility (UtA-PI) and umbilical artery doppler pulsatility index (UA-PI) over gestation.

Methods: Nulliparous women with a singleton pregnancy participating in a prospective cohort study (n=4212) underwent serial UtA-PI and UA-PI measurements at 20-, 28- and 36-weeks gestation. Linear mixed regression models were employed to investigate the influence of maternal BMI, fetal sex and interactions thereof on the magnitude of change in UtA-PI and UA-PI.

Results: Throughout gestation, UtA-PI was higher for male fetuses and UA-PI was higher for female fetuses. The physiological drop of UtA-PI was significantly smaller in overweight (change -24.3% [95% confidence interval (CI) -22.3, -26.2]) and obese women (change -21.3% [-18.3, -24.3]), compared to normal weight women (change -25.7% [-24.3, -27.0]) but did not differ by fetal sex. The physiological drop in UA-PI was greater for female than male fetuses (-32.5% [-31.5, -33.5] vs. -30.7% [-29.8, -31.7]) but did not differ by maternal BMI. No interactions between maternal BMI and fetal sex were found.

Conclusion: Maternal cardiovascular adaptation to pregnancy is independently associated with maternal BMI and fetal sex. These results imply sexual dimorphism in both maternal cardiovascular adaptation and feto-placental resistance.

4.2 Background

Successful pregnancy requires the de novo creation of low resistance utero-placental and feto-placental circulations. Incomplete remodelling of the maternal spiral arteries or failure to form a sufficiently low-resistance placental circulation results in fetal and maternal compromise, and subsequent adverse outcomes, including preeclampsia [286, 287, 121] and fetal growth restriction [121, 288, 127]. Doppler ultrasonography can be used in pregnancy to assess the utero-placental and feto-placental circulation, with the uterine artery doppler pulsatility index (PI) reflecting vascular resistance on the maternal side of the placental circulation [289] and the umbilical artery PI reflecting the vascular resistance on the fetal side of the placenta [290, 291]. In the non-pregnant state, obesity impairs vascular compliance and is associated with increased arterial stiffness [292, 293]. In pregnancy, high maternal BMI is associated with increased systolic blood pressure, increased left ventricular mass, and higher stroke volume [294–296], even in pregnant obese women without perinatal complications [297, 298]. Women with a higher BMI have a ‘dose-dependent’ increased risk of incomplete spiral artery conversion during pregnancy, which is likely to impair the formation of an appropriately low-resistance utero-placental circulation [152]

Fetal sex is also increasingly recognised as a key modulator of both placental development and maternal adaptation to pregnancy [299, 282, 300]. Recent evidence suggests that fetal sex differences influence the production of maternal angiogenic and fibrinolytic factors (e.g. sFlt-1, PlGF), which are known for their associations with placental development and placental vascular adaptation to pregnancy [301, 302]. Broere-Brown and colleagues observed sex differences in ultrasonographic measurements of maternal vascular resistance; women pregnant with a male fetus had higher uterine artery pulsatility index (UtA-PI) in the second and third trimester compared to women carrying a female fetus [303]. Further evidence suggests that the umbilical artery pulsatility index (UA-PI) is higher in pregnancies where the fetus is female compared to male [304].

The aim of the present study was to define the longitudinal impact of maternal BMI and fetal sex on resistance in the utero-placental and feto-placental circulation, and in particular whether these are synergistic or independent factors. Crucially, both of these factors can vary between different pregnancies in the same woman. BMI changes between subsequent pregnancies are relatively common and alter the risk of an adverse pregnancy outcome [254]. Fetal sex is determined as-if-at-random for each pregnancy and is also an important influence on pregnancy success [305, 306]. Our findings may therefore help to explain variability in pregnancy complications experienced by women in successive pregnancies.

4.3 Methods

Women from the Pregnancy Outcome Prediction Study (POPS) were included in this analysis. The description of the POPS study design, inclusion criteria and general definitions can be found in Chapter 3.

4.3.1 Definitions specific for this analysis

Uterine artery dopplers were quantified at the 20, 28- and 36-weeks scan as the mean PI of the left and right uterine arteries. Umbilical artery dopplers were quantified at the 20, 28- and 36-weeks scan. The cut off values for clinically relevant reference ranges of the pulsatility indices (PI) used were (i) uterine artery PI $>95^{th}$ centile at 20 wkGA (ii) umbilical artery PI $>95^{th}$ centile at 28 wkGA and (iii) umbilical artery PI $>95^{th}$ centile at 36 wkGA.

4.3.2 Doppler measurements

The UtA-PI was assumed to reflect the resistance in the utero-placental circulation and thus the efficacy of spiral artery remodelling [286], with a higher UtA-PI indicating narrow and stiff spiral arteries [307]. The UA-PI was assumed to primarily reflect resistance in the fetoplacental circulation (although it will also depend on fetal cardiac function [308, 309]).

4.3.3 Data analysis

As the Doppler measurements for the UtA-PI and UA-PI were not normally distributed, they were log-transformed before used in the model. To account for non-independence of the repeated measured pulsatility indices (multiple measurements in the same woman), linear mixed regression analyses were used to model the absolute log-transformed UtA-PI or UA-PI measurements to assess the changes in UtA-PI or UA-PI levels over gestation. The linear mixed models included a random intercept per woman, fixed effects for BMI category and/or fetal sex (and interactions thereof) at the estimated gestational age at each research scanning time (i.e. 20, 28 or 36 weeks). Further adjustment was made for maternal systolic blood pressure measured at 12 weeks, maternal ethnicity, maternal age, marital status, maternal smoking status and deprivation index. Covariates were selected based on clinical relevance. The β -coefficient output from the mixed linear model was transformed to a percentage change between scanning timepoints to allow for easier interpretation. The model used to estimate the unadjusted log transformed levels of UtA-PI over gestation by BMI categories can be represented as:

$$\log(UtA - Pl_{ij}) = \text{NORMAL WEIGHT}_i \times \sum_{j=1}^3 \beta_{0j} d_{ij} + \text{OVERWEIGHT}_i \times \sum_{j=1}^3 \beta_{1j} d_{ij} + \text{OBESE}_i \times \sum_{j=1}^3 \beta_{2j} d_{ij} \quad (4.1)$$

where d_{i1} equals the estimated gestational age at the 20-week scan minus 20, d_{i2} represents the estimated gestational age at the 28-week scan minus 28 and d_{i3} represents the estimated gestational age at the 36-week scan minus 36; u_i represents the random intercept and e_{ij} represents residual error for individual i and scanning time j for $j=1, \dots, 3$. This parameterisation allows easy interpretation, for example, β_{01} , β_{02} and β_{03} represent the log-transformed values in UtA-PI at exactly 20, 28 or 36 weeks, respectively for normal weight women.

As a sensitivity analysis, we repeated the analyses to (i) include glucose measurement at 28 weeks, (ii) add gestational weight gain as covariates and (iii) exclude women who experienced any perinatal complication during pregnancy (gestational diabetes, preeclampsia, gestational hypertension or preterm birth).

Statistical analyses were performed using R [310] with the lme4 package [311] for performing mixed linear models. Figures were produced using the ggplot2 package [312].

4.4 Results

A total of 4512 women enrolled in the POP study, with 300 women lost to follow up. For this analysis, we excluded women with missing information on maternal BMI and/or fetal sex ($n=19$), with a stillbirth or miscarriage ($n=33$), with missing information on covariates ($n=351$) and who were underweight ($n=67$), since the underweight group was underpowered for inference (Figure 4.1).

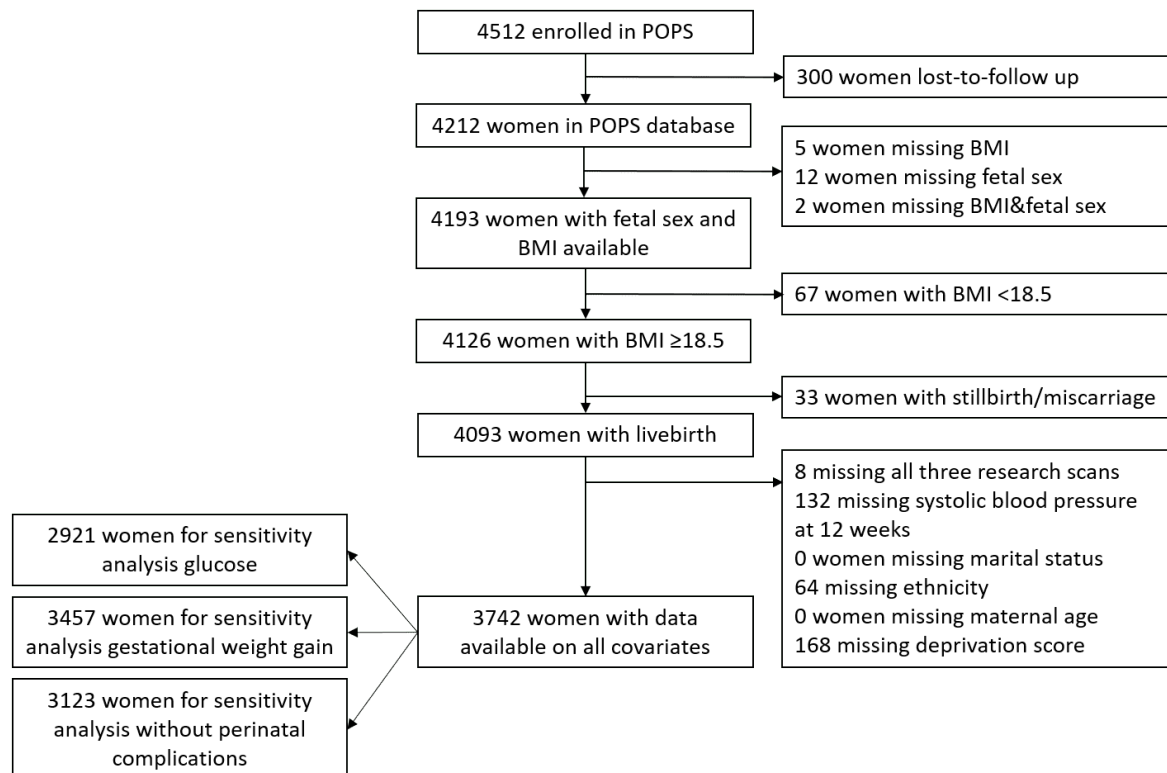


Fig. 4.1 Flow diagram showing in- and exclusion criteria. The final population available for analysis was 3742 women. POPS; Pregnancy Outcome Prediction Study, BMI; Body Mass Index.

A total of 3742 women were included in the analyses, of whom 57.8% had a normal weight (BMI 18.5-24.9 kg/m²), 28.3% were overweight (BMI 25.0-29.9 kg/m²), and 13.9% were classified as obese (BMI ≥30.0 kg/m²) (Table 4.1). Women with higher maternal BMI were more likely to be smokers, and have pre-existing and gestational hypertension, as well as preeclampsia and gestational diabetes. Neonates born to overweight and obese women were more likely to have higher birthweight and placental weight compared to babies born to normal weight women (Table 4.1). There were no significant differences in maternal baseline characteristics or perinatal complications between fetal sexes. Male neonates had on average about 125g higher birthweight compared to female neonates (Table 4.2).

	Normal weight n=2164	Overweight n=1059	Obese n=519	Total n=3742
Maternal age (y)	30.0 (4.8)	30.4 (5.3)	29.3 (5.7)	30.0 (5.1)
Gestational age at first scan (week)	12.6 (0.8)	12.6 (0.8)	12.9 (0.6)	12.9 (0.9)
Gestational weight gain* (kg)				
Total weight gain	12.4 (3.7)	12.8 (4.5)	10.8 (5.4)	12.3 (4.2)
From 12 to 20 weeks	3.4 (2.1)	3.2 (2.2)	2.6 (2.4)	3.2 (2.2)
From 20 to 28 weeks	4.7 (2.2)	4.9 (2.3)	4.0 (2.3)	4.6 (2.3)
From 28 to 36 weeks	4.3 (2.3)	4.6 (2.4)	4.2 (2.7)	4.4 (2.4)
Smoking status				
Non-smoker	1381 (63.8)	592 (55.9)	266 (51.3)	2239 (59.8)
Quit pre-pregnancy	536 (24.8)	330 (31.2)	161 (31.0)	1027 (27.4)
Quit during pregnancy	143 (6.6)	93 (8.8)	58 (11.2)	294 (7.9)
Current smokers	104 (4.8)	44 (4.2)	34 (6.6)	182 (4.9)
Systolic BP (12 wkGA (mmHg))	106.5 (11)	109.4 (11)	114.5 (11)	108.4 (11)
Fetal sex				
Male	1090 (50.4)	531 (50.1)	264 (50.9)	1885 (50.4)
Female	1074 (49.6)	528 (49.9)	255 (49.1)	1857 (49.6)
Maternal ethnicity				
White	2027 (93.7)	1005 (94.9)	498 (96.0)	3530 (94.3)
Other	137 (6.3)	54 (5.1)	21 (4.0)	212 (5.7)
Marital status				
Married	1535 (70.9)	718 (67.8)	316 (60.9)	2569 (68.7)
Not married	629 (29.1)	341 (32.2)	203 (39.1)	1173 (31.3)
Deprivation score				
1 (lowest)	555 (25.6)	282 (26.6)	112 (21.6)	949 (25.4)
2)	518 (23.9)	276 (26.1)	128 (24.7)	922 (24.6)
3)	541 (25.0)	271 (25.6)	132 (25.4)	944 (25.2)
4 (highest)	550 (25.4)	230 (21.7)	147 (28.3)	927 (24.8)
Pre-existing diabetes				
Yes	4 (0.2)	10 (0.9)	2 (0.4)	16 (0.4)
No	2160 (99.8)	1049 (99.1)	517 (99.6)	3726 (99.6)
Pre-existing hypertension				
Yes	64 (3.0)	68 (6.4)	67 (12.9)	199 (5.3)
No	2100 (97.0)	991 (93.6)	452 (87.1)	3543 (94.7)
Gestational hypertension				
Yes	24 (1.1)	23 (2.2)	20 (3.9)	67 (1.8)
No	2138 (98.8)	1035 (97.7)	499 (96.1)	3672 (98.1)
Unknown	2 (0.1)	1 (0.1)	0 (0.0)	3 (0.1)
Preeclampsia				
Yes	95 (4.4)	76 (7.2)	84 (16.2)	255 (6.8)
No	2067 (95.5)	982 (92.7)	435 (83.8)	3484 (93.1)
Unknown	2 (0.1)	1 (0.1)	0 (0.0)	3 (0.1)
Gestational diabetes				
Yes	58 (2.7)	62 (5.9)	57 (11.0)	177 (4.7)
No	2105 (97.3)	993 (93.8)	462 (89.0)	3560 (95.1)
Unknown	1 (0.0)	4 (0.4)	0 (0.0)	5 (0.1)
Birthweight (g)	3380 (498)	3444 (519)	3498 (569)	3414 (516)
Placental weight (g)	451 (93)	473 (102)	490 (489)	463 (99)

Table 4.1 Baseline and birth characteristics stratified by maternal BMI category. Data are represented as mean (SD) or as number (%). BP; blood pressure, wkGA; weeks gestational age. Differences in baseline characteristics were tested using chi-square tests and Kruskal-Wallis tests. *n-number for gestational weight gain at (i) 12-20wk; normal weight 2139, overweight 1048 and obese 515, (ii) 20-28wk; normal weight 2085, overweight 1024 and obese 505, (iii) 28-36 wk; normal weight 1991, overweight 955 and obese 465, (iv) 12-36wk; normal weight 2021, overweight 965 and obese 471.

	Male fetus n=1885	Female fetus n=1857	Total n=3742
Maternal age (y)	30.1 (5.1)	29.9 (5.1)	30.0 (5.1)
Gestational age at first scan (w)	12.7 (0.8)	12.6 (0.9)	12.9 (0.9)
Gestational weight gain* (kg)			
Total weight gain	12.4 (4.3)	12.1 (4.1)	12.3 (4.2)
From 12 to 20 weeks	3.3 (2.2)	3.2 (2.1)	3.2 (2.2)
From 20 to 28 weeks	4.7 (2.3)	4.6 (2.2)	4.6 (2.3)
From 28 to 36 weeks	4.4 (2.4)	4.3 (2.3)	4.4 (2.4)
Smoking status			
Non-smoker	1151 (61.1)	1088 (58.6)	2239 (59.8))
Quit prepregnancy	486 (25.8)	541 (29.1)	1027 (27.4)
Quit during pregnancy	149 (7.9)	145 (7.8)	294 (7.9)
Current smokers	99 (5.3)	83 (4.5)	182 (9.8)
Systolic BP (12 wkGA (mmHg))	108.5 (12)	108.3 (11)	108.4 (11)
Maternal BMI category			
Normal weight	1090 (57.8)	1074 (57.8)	2164(57.8)
Overweight	531 (28.2)	528 (28.4)	1059 (28.3)
Obese	264 (14.0)	255 (13.7)	519 (27.9)
Maternal ethnicity			
White	1773 (94.1)	1757 (94.6)	3530 (94.3)
Other	112 (5.9)	100 (5.4)	212 (5.7)
Marital status			
Married	1297 (68.8)	1272 (68.5)	2569 (68.7)
Not married	588 (31.2)	585 (31.5)	1173 (31.3)
Deprivation score			
1 (lowest)	495 (26.3)	454 (24.4)	949 (25.4)
2)	452 (24.0)	470 (25.3)	922 (24.6)
3)	465 (24.7)	479 (25.8)	944 (25.2)
4 (highest)	473 (25.1)	454 (24.4)	927 (24.8)
Pre-existing diabetes			
Yes	7 (0.4)	9 (0.5)	16 (0.4)
No	1878 (99.6)	1848 (99.5)	3726 (99.6)
Pre-existing hypertension			
Yes	106 (5.6)	93 (5.0)	199 (5.3)
No	1779 (94.4)	1764 (95.0)	3543 (94.7)
Gestational hypertension			
Yes	35 (1.9)	32 (1.7)	67 (1.8)
No	1848 (98.0)	1824 (98.2)	3672 (98.1)
Unknown	2 (0.1)	1 (0.1)	3 (0.1))
Preeclampsia			
Yes	138 (7.3)	117 (6.3)	255 (6.8)
No	1745 (92.6)	1739 (93.6)	3484 (93.1)
Unknown	2 (0.1)	1 (0.1)	3 (0.1))
Gestational diabetes			
Yes	96 (5.1)	81 (4.4)	177 (4.7)
No	1786 (94.7)	1774 (95.5)	3560 (95.1)
Unknown	3 (0.2)	2 (0.1)	5 (0.1)
Birthweight (g)	3477 (529)	3350 (494)	3414 (516)
Placental weight (g)	465 (99)	461 (99)	463 (99)

Table 4.2 Baseline and birth characteristics stratified by fetal sex. Data are represented as mean (SD) or as number (%). BP; blood pressure, wkGA; weeks gestational age. Differences in baseline characteristics were tested using chi-square tests and Kruskal-Wallis tests. *n-number for gestational weight gain at (i) 12-20wk; male fetus 1866, female fetus 1836 (ii) 20-28wk; male fetus 1814, female fetus 1800, (iii) 28-36 wk; male fetus 1709, female fetus 1702, (iv) 12-36wk; male fetus 1732, female fetus 1725.

The absolute values of UtA-PI were similar between normal, overweight and obese women at the 20-week scan (Figure 4.2). The physiological drop in UtA-PI between 20 and 36 weeks was lower in obese women compared to women of normal weight (mean drop -21.3% [95% CI -18.3, -24.2] vs -25.7% [-24.3, -27.0], respectively, $p < 0.001$) (Table 4.3), which remained after correction for maternal variables including maternal BMI, systolic blood pressure at 12 weeks gestation, marital status, maternal age, maternal ethnicity and deprivation index. This overall decrease in physiological drop is due to a diminished fall in resistance in the early phase (20 to 28 weeks), rather than the later phase (28 to 36 weeks).

UtA-PI was higher throughout gestation for women carrying a male versus female fetus (Figure 4.2). Fetal sex did not significantly influence the magnitude of the drop in uterine artery PI over gestation (Table 4.4). There was no evidence of an interaction between fetal sex and maternal BMI on UtA-PI over gestation (Table 4.5).

Women carrying a female fetus had a higher UA-PI throughout all of gestation compared to women carrying a male fetus (Figure 4.3). The overall drop in UA-PI between 20 and 36 weeks was greater in women carrying a female fetus compared to a male fetus (-32.5% [-31.5, -33.5] vs -30.7% [-29.8, -31.7], respectively, $p < 0.001$) (Table 4.6). We did not observe any differences in umbilical artery pulsatility indices or the drop in UA-PI between maternal BMI categories (Figure 4.3 and Table 4.7). We did not find any sexual dimorphism in the relationship between UA-PI and maternal prepregnancy BMI (Table 4.8).

A total of 5% of women had a UtA-PI value $>95^{th}$ centile at 20 wkGA; 5.3% of normal weight women were above the reference range, while 4.9% of overweight and 4.0% of obese women had UtA-PI values $>95^{th}$ centile at 20 wkGA (chi-square test p -value = 0.50). At 28 wkGA, 5.0% of women had a UA-PI value $>95^{th}$ centile; 4.4% of the women carrying a male fetus and 5.6% of the women carrying a female fetus were above the reference range (chi-square test p -value = 0.28). The same pattern was seen at 36 wkGA for a UA-PI value $>95^{th}$ centile; 4.7% of all women, 4.3% of women carrying a male fetus and 5.1% of women carrying a female fetus had a UA-PI $>95^{th}$ centile at 36 wkGA (chi-square test p -value = 0.78).

Results for the sensitivity analysis investigating the influence of glucose levels at 28 weeks gestation or gestational weight gain, as well as excluding women with gestational diabetes, preeclampsia, gestational hypertension and preterm birth were unchanged from the main analysis (Tables 4.9, 4.10 and 4.11).

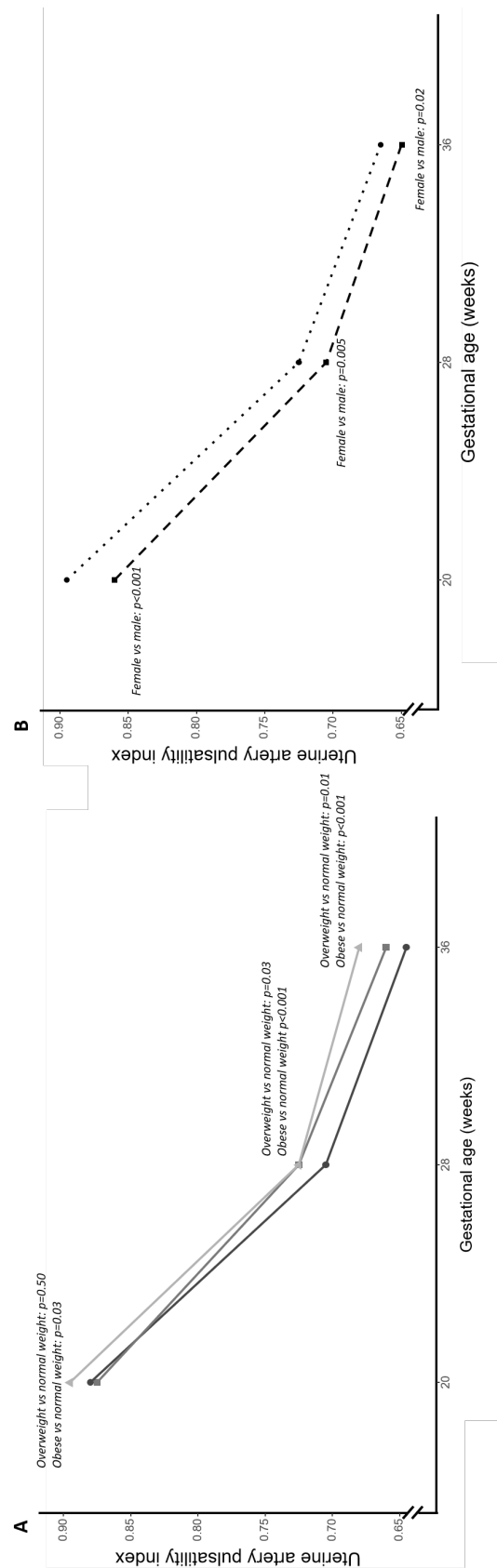


Fig. 4.2 (A) Development of uterine artery pulsatility index (UtA-PI) over gestation stratified by maternal BMI category. Absolute values at scanning timepoints [median (IQR)]; 20 wks [0.88 (0.72-1.09)], 28 wks [0.71 (0.61-0.84)], 36 wks [0.65 (0.56-0.77)]. Overweight women; 20 wks [0.88 (0.73-1.08)], 28 wks [0.73 (0.62-0.85)], 36 wks [0.66 (0.56-0.78)]. Obese women; 20wks [0.90 (0.74-1.09)], 28 wks [0.73 (0.63-0.88)], 36 wks [0.68 (0.59-0.82)]. Black; women with normal weight, dark grey; overweight women, light grey; obese women. (B) Development of UtA-PI over gestation stratified by fetal sex. Absolute values at scanning timepoints [median (IQR)]; 20 wks [0.90 (0.74-1.10)], 28 wks [0.73 (0.62-0.86)], 36 wks [0.67 (0.58-0.78)]. Female fetuses; 20 wks [0.86 (0.71-1.07)], 28wks [0.71 (0.60-0.84)], 36 wks [0.65 (0.55-0.77)]. Dashed line; women carrying female fetus, dotted line; women carrying male fetus. Estimates are simple observed medians at each scanning time, statistics shown are from mixed linear model corrected for gestational age. All p-values are compared to normal weight women at same time period or women carrying a male fetus at the same time period.

	Drop between 20- and 36-week scan				Drop between 20- and 28-week scan				Drop between 28- and 36-week scan			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*
Normal weight n=2164	-25.7% -24.3, -27.0	ref	-25.7% -24.3, -27.0	ref	-19.7% -18.3, -21.0	ref	-19.7% -18.3, -21.0	ref	-7.4% -6.1, -8.8	ref	-7.4% -6.1, -8.8	ref
Overweight (n=1059)	-24.3% -22.3, -26.2	0.13	-24.3% -22.3, -26.3	0.13	-17.9% -16.0, -19.8	0.07	-17.9% -16.0, -19.8	0.07	-7.7% -5.8, -9.7	0.79	-7.7% -5.8, -9.7	0.79
Obese (n=519)	-21.3% -18.3, -24.3	<0.001	-21.3% -18.3, -24.2	<0.001	-16.4% -13.5, -19.3	0.01	-16.4% -13.5, -19.3	0.01	-5.8% -2.8, -8.8	0.30	-5.8% -2.8, -8.8	0.30

Table 4.3 Percentage change in uterine artery pulsatility index over the course of gestation by maternal BMI category, expressed as percentage drop of Doppler PI between scanning timepoints. CI; Confidence Interval. Model 1 adjusted for gestational age at all scanning timepoints. Model 2 adjusted for gestational age at all scanning timepoints, maternal BMI, systolic blood pressure at 12 weeks gestation, marital status, maternal age, maternal ethnicity, maternal smoking status and deprivation index. *p-value relative to mean uterine artery pulsatility index drop in normal weight women at same scanning timepoint.

	Drop between 20- and 36-week scan				Drop between 20- and 28-week scan				Drop between 28- and 36-week scan			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*
Male fetus (n=1885)	-24.9% -23.5, -26.4	ref	-24.9% -23.5, -26.4	ref	-19.1% -17.6, -20.5	ref	-19.1% -17.6, -20.6	ref	-7.2% -5.7, -8.7	ref	-7.2% -5.7, -8.7	ref
Female fetus (n=1857)	-24.5% -23.0, -26.0	0.57	-24.5% -23.0, -26.0	0.55	-18.4% -16.9, -19.9	0.43	-18.4% -16.9, -19.9	0.42	-7.5% -6.0, -9.0	0.83	-7.5% -5.9, -8.9	0.84

Table 4.4 Percentage change in uterine artery pulsatility index over the course of gestation by fetal sex, expressed as percentage drop of Doppler PI between scanning timepoints. CI; Confidence Interval. Model 1 adjusted for gestational age at all scanning timepoints. Model 2 adjusted for gestational age at all scanning timepoints, maternal BMI, systolic blood pressure at 12 weeks gestation, marital status, maternal age, maternal ethnicity, maternal smoking status and deprivation index. *p-value relative to mean uterine artery pulsatility index drop in normal weight women at same scanning timepoint.

	Drop between 20- and 36-week scan						Drop between 20- and 28-week scan						Drop between 28- and 36-week scan					
	Model 1			Model 2			Model 1			Model 2			Model 1			Model 2		
	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]
Male fetus	Normal weight (n=1090)	-25.7% -23.8, -27.6	ref	-25.7% -23.8, -27.6	ref	-20.1% -18.2, -22.0	-20.1% -18.2, -22.0	ref	-20.1% -18.2, -22.0	ref	-20.1% -18.2, -22.0	-20.1% -18.2, -22.0	ref	-7.1% -5.1, -9.0	-7.1% -5.1, -9.0	ref	-7.1% -5.1, -9.0	ref
	Overweight (n=531)	-25.4% -22.6, -28.2	0.79	-25.4% -22.6, -28.2	0.79	-18.2% -15.4, -20.9	-18.2% -15.4, -20.9	0.17	-18.2% -15.4, -20.9	0.17	-18.2% -15.4, -20.9	-18.2% -15.4, -20.9	0.17	-8.8% -6.0, -11.6	-8.8% -6.0, -11.6	0.28	-8.8% -6.0, -11.6	0.28
	Obese (n=264)	-20.3% -16.2, -24.5	0.002	-20.3% -16.1, -24.5	0.002	-16.6% -12.5, -20.7	-16.6% -12.5, -20.7	0.06	-16.6% -12.5, -20.7	0.06	-16.5% -12.6, -20.6	-16.5% -12.6, -20.6	0.06	-4.5% -0.3, -8.7	-4.5% -0.3, -8.7	0.24	-4.5% -0.3, -8.7	0.24
Female fetus	Normal weight (n=1074)	-25.5% -23.6, -27.5	ref	-25.5% -23.6, -27.5	ref	-19.2% -17.3, -21.2	-19.2% -17.3, -21.2	ref	-19.2% -17.3, -21.2	ref	-19.2% -17.3, -21.2	-19.2% -17.3, -21.2	ref	-7.8% -5.9, -9.8	-7.8% -5.9, -9.8	ref	-7.8% -5.9, -9.8	ref
	Overweight (n=528)	-23.1% -20.3, -26.0	0.06	-23.1% -20.3, -26.0	0.06	-17.6% -14.9, -20.4	-17.6% -14.9, -20.4	0.24	-17.6% -14.9, -20.4	0.24	-17.6% -14.9, -20.4	-17.6% -14.9, -20.4	0.24	-6.7% -3.9, -9.5	-6.7% -3.9, -9.5	0.49	-6.7% -3.9, -9.5	0.49
	Obese (n=255)	-22.3% -18.0, -26.6	0.07	-22.2% -18.0, -26.5	0.06	-16.3% -12.1, -20.5	-16.3% -12.1, -20.5	0.12	-16.2% -12.1, -20.4	0.11	-16.2% -12.1, -20.4	-16.2% -12.1, -20.4	0.11	-7.2% -2.8, -11.5	-7.2% -2.8, -11.5	0.76	-7.2% -2.8, -11.5	0.76

Table 4.5 Percentage change in uterine artery pulsatility index over the course of gestation by fetal sex and maternal BMI category, expressed as percentage drop of Doppler PI between scanning timepoints. CI: Confidence Interval. Model 1 adjusted for gestational age at all scanning timepoints. Model 2 adjusted for gestational age at all scanning timepoints, maternal BMI, systolic blood pressure at 12 weeks gestation, marital status, maternal age, maternal ethnicity, maternal smoking status and deprivation index. * p-value relative to mean uterine artery pulsatility index drop in normal weight women at same scanning timepoint.

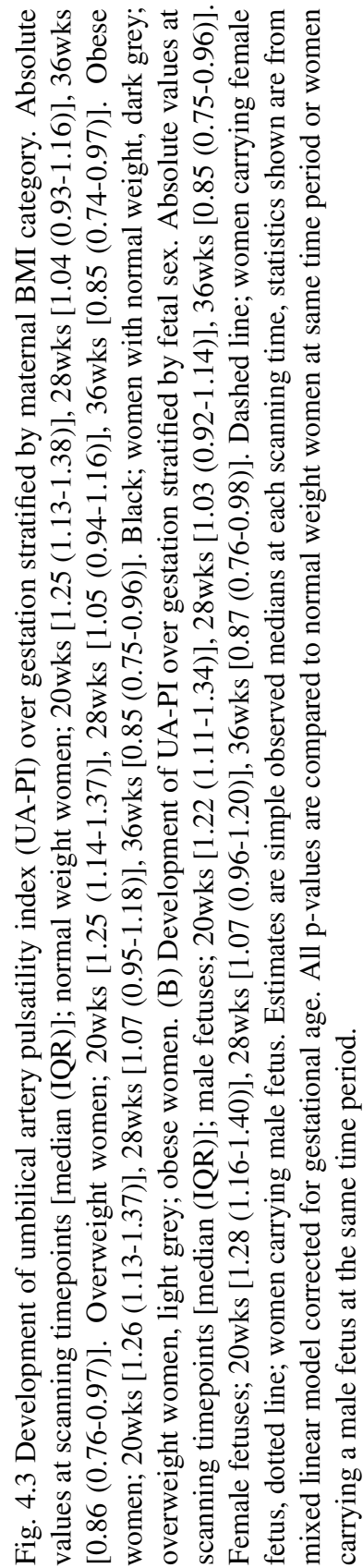


Fig. 4.3 Development of umbilical artery pulsatility index (UA-PI) over gestation stratified by maternal BMI category. Absolute values at scanning timepoints [median (IQR)]; normal weight women; 20wks [1.25 (1.13-1.38)], 28wks [1.04 (0.93-1.16)], 36wks [0.86 (0.76-0.97)]. Overweight women; 20wks [1.25 (1.14-1.37)], 28wks [1.05 (0.94-1.16)], 36wks [0.85 (0.74-0.97)]. Obese women; 20wks [1.26 (1.13-1.37)], 28wks [1.07 (0.95-1.18)], 36wks [0.85 (0.75-0.96)]. Black; women with normal weight, dark grey; overweight women, light grey; obese women. (B) Development of UA-PI over gestation stratified by fetal sex. Absolute values at scanning timepoints [median (IQR)]; male fetuses; 20wks [1.22 (1.11-1.34)], 28wks [1.03 (0.92-1.14)], 36wks [0.85 (0.75-0.96)]. Female fetuses; 20wks [1.28 (1.16-1.40)], 28wks [1.07 (0.96-1.20)], 36wks [0.87 (0.76-0.98)]. Dashed line; women carrying female fetus, dotted line; women carrying male fetus. Estimates are simple observed medians at each scanning time, statistics shown are from mixed linear model corrected for gestational age. All p-values are compared to normal weight women at same time period or women carrying a male fetus at the same time period.

	Drop between 20- and 36-week scan				Drop between 20- and 28-week scan				Drop between 28- and 36-week scan			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*
Male fetus (n=1885)	-30.7% -29.8, -31.7	ref	-30.7% -29.8, -31.7	ref	-16.4% -15.4, -17.3	ref	-16.4% -15.4, -17.3	ref	-17.2% -16.2, -18.2	ref	-17.2% -16.2, -18.2	ref
Female fetus (n=1857)	-32.5% -31.5, -33.5	<0.001	-32.5% -31.5, -33.5	<0.001	-16.8% -15.8, -17.7	0.46	-16.8% -15.8, -17.7	0.46	-18.9% -17.9, -19.8	0.004	-18.9% -17.9, -19.8	0.004

Table 4.6 Percentage change in umbilical artery pulsatility index over the course of gestation fetal sex, expressed as percentage drop of Doppler PI between scanning timepoints. CI; Confidence Interval. Model 1 adjusted for gestational age at all scanning timepoints. Model 2 adjusted for gestational age at all scanning timepoints, maternal BMI, systolic blood pressure at 12 weeks gestation, marital status, maternal age, maternal ethnicity, maternal smoking status and deprivation index. * p-value relative to mean umbilical artery pulsatility index drop in normal weight women at same scanning timepoint.

	Drop between 20- and 36-week scan				Drop between 20- and 28-week scan				Drop between 28- and 36-week scan			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*
Normal weight (n=2164)	-31.2% -30.3, -32.1	ref	-31.2% -30.3, -32.1	ref	-16.8% -15.9, -17.7	ref	-16.8% -15.9, -17.7	ref	-17.3% -16.4, -18.2	ref	-17.3% -16.4, -18.2	ref
Overweight (n=1059)	-32.2% -30.9, -33.6	0.06	-32.2% -30.9, -33.6	0.06	-16.4% -15.1, -17.7	0.54	-16.4% -15.1, -17.7	0.54	-18.9% -17.6, -20.2	0.01	-18.9% -17.6, -20.2	0.01
Obese (n=519)	-31.9% -30.0, -33.8	0.32	-31.9% -30.0, -33.8	0.32	-15.7% -13.8, -17.6	0.22	-15.7% -13.8, -17.6	0.22	-19.2% -17.3, -21.1	0.03	-19.2% -17.3, -21.1	0.03

Table 4.7 Percentage change in umbilical artery pulsatility index over the course of gestation by maternal BMI category, expressed as percentage drop of Doppler PI between scanning timepoints. CI; Confidence Interval. Model 1 adjusted for gestational age at all scanning timepoints. Model 2 adjusted for gestational age at all scanning timepoints, maternal BMI, systolic blood pressure at 12 weeks gestation, marital status, maternal age, maternal ethnicity, maternal smoking status and deprivation index. *p-value relative to mean umbilical artery pulsatility index drop in normal weight women at same scanning timepoint.

	Drop between 20- and 36-week scan				Drop between 20- and 28-week scan				Drop between 28- and 36-week scan			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*
Male fetus (n=1090)	-30.5% -29.2, -31.7	ref	-30.5% -29.2, -31.7	ref	-16.5% -15.3, -17.8	ref	-16.5% -15.3, -17.8	ref	-16.7% -15.5, 18.0	ref	-16.7% -15.5, 18.0	ref
Female fetus (n=1074)	-32.0% -30.7, -33.2	0.02	-32.0% -30.7, -33.2	0.02	-17.1% -15.9, -18.4	0.40	-17.1% -15.9, -18.4	0.40	-17.9% -16.6, -19.2	0.13	-17.9% -16.6, -19.2	0.13
Male fetus (n=531)	-31.0% -29.1, -32.8	ref	-31.0% -29.1, -32.8	ref	-15.9% -14.1, -17.7	ref	-15.9% -14.1, -17.7	ref	-17.9% -16.0, -19.8	ref	-17.9% -16.0, -19.8	ref
Female fetus (n=528)	-33.5% -31.6, -35.3	0.006	-33.5% -31.6, -35.3	0.006	-16.9% -15.1, -18.7	0.36	-16.9% -15.1, -18.7	0.36	-19.9% -18.1, -21.8	0.06	-19.9% -18.1, -21.8	0.06
Male fetus (n=264)	-31.3% -28.5, -34.0	ref	-31.3% -28.5, -34.0	ref	-16.6% -13.8, -19.3	ref	-16.6% -13.8, -19.3	ref	-17.6% -14.8, -20.4	ref	-17.6% -14.8, -20.4	ref
Female fetus (n=255)	-32.7% -29.8, -35.5	0.31	-32.6% -29.8, -35.5	0.32	-14.9% -12.1, -17.7	0.30	-14.9% -12.1, -17.7	0.30	-20.9% -18.0, -23.7	0.04	-20.9% -18.0, -23.7	0.04

Table 4.8 Percentage change in umbilical artery pulsatility index over the course of gestation by maternal BMI category and fetal sex, expressed as percentage drop of Doppler PI between scanning timepoints. CI: Confidence Interval. Model 1 adjusted for gestational age at all scanning timepoints. Model 2 adjusted for gestational age at all scanning timepoints, maternal BMI, systolic blood pressure at 12 weeks gestation, marital status, maternal age, maternal ethnicity, maternal smoking status and deprivation index. * p-value relative to mean umbilical artery pulsatility index drop in normal weight women at same scanning timepoint.

	Drop between 20- and 36-week scan				Drop between 20- and 28-week scan				Drop between 28- and 36-week scan			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*
Normal weight n=1649	-26.2% -24.7, -27.7	ref	-26.2% -24.7, -27.7	ref	-20.3% -18.8, -21.8	ref	-20.3% -18.8, -21.8	ref	-7.4% -5.9, -9.0	ref	-7.4% -5.9, -9.0	ref
Overweight (n=771)	-24.3% -22.0, -26.5	0.06	-24.3% -22.0, -26.5	0.06	-18.2% -16.0, -20.5	0.06	-18.2% -16.0, -20.5	0.06	-7.4% -5.1, -9.6	0.97	-7.4% -5.1, -9.6	0.97
Obese (n=313)	-20.8% -17.1, -24.5	<0.001	-20.8% -17.1, -24.5	<0.001	-17.8% -14.1, -21.5	0.12	-17.8% -14.1, -21.5	0.12	-3.7% 0.0, -7.4	0.05	-3.7% 0.0, -7.4	0.05

Table 4.9 Sensitivity analysis of the effect of glucose levels at 28 weeks on the percentage change in uterine artery pulsatility index over the course of gestation by maternal BMI category, expressed as percentage drop of Doppler PI between scanning timepoints. CI; Confidence Interval. Model 1 adjusted for gestational age at all scanning timepoints. Model 2 adjusted for gestational age at all scanning timepoints, maternal BMI, systolic blood pressure at 12 weeks gestation, marital status, maternal age, maternal ethnicity, maternal smoking status and deprivation index. *p-value relative to mean uterine artery pulsatility index drop in normal weight women at same scanning timepoint.

	Drop between 20- and 36-week scan				Drop between 20- and 28-week scan				Drop between 28- and 36-week scan			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*
Normal weight n=2008	-25.7% -24.3, -27.1	ref	-25.7% -24.3, -27.1	ref	-19.8% -18.5, -21.1	ref	-19.8% -18.5, -21.1	ref	-7.3% -5.9, -8.7	ref	-7.3% -5.9, -8.7	ref
Overweight (n=962)	-24.4% -22.4, -26.5	0.17	-24.4% -22.4, -26.5	0.17	-18.2% -16.2, -20.3	0.11	-18.2% -16.2, -20.3	0.11	-7.6% -5.5, -9.6	0.82	-7.6% -5.5, -9.6	0.82
Obese (n=469)	-21.1% -18.0, -24.1	<0.001	-21.1% -18.0, -24.1	<0.001	-16.4% -13.3, -19.4	0.01	-16.3% -13.3, -19.4	0.01	-5.6% -2.5, -8.7	0.28	-5.6% -2.5, -8.7	0.28

Table 4.10 Sensitivity analysis of the effect of gestational weight gain between 12 and 36 weeks on the percentage change in uterine artery pulsatility index over the course of gestation by maternal BMI category, expressed as percentage drop of Doppler PI between scanning timepoints. CI; Confidence Interval. Model 1 adjusted for gestational age at all scanning timepoints. Model 2 adjusted for gestational age at all scanning timepoints, maternal BMI, systolic blood pressure at 12 weeks gestation, marital status, maternal age, maternal ethnicity, maternal smoking status and deprivation index. *p-value relative to mean uterine artery pulsatility index drop in normal weight women at same scanning timepoint.

	Drop between 20- and 36-week scan				Drop between 20- and 28-week scan				Drop between 28- and 36-week scan			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*	Percentage decrease [95% CI]	p value*
Normal weight n=1906	-25.5% -24.1, -27.0	ref	-25.5% -24.1, -27.0	ref	-19.5% -18.1, -20.9	ref	-19.5% -18.1, -20.9	ref	-7.5% -6.1, -8.9	ref	-7.5% -6.1, -8.9	ref
Overweight (n=856)	-24.2% -22.1, -26.4	0.19	-24.2% -22.1, -26.4	0.19	-17.5% -15.4, -19.6	0.06	-17.5% -15.4, -19.6	0.06	-8.2% -6.0, -10.3	0.58	-8.2% -6.0, -10.3	0.58
Obese (n=361)	-21.2% -17.8, -24.7	0.003	-21.2% -17.7, -24.7	0.003	-16.2% -12.8, -19.7	0.03	-16.2% -12.8, -19.7	0.03	-5.9% -2.5, -9.4	0.37	-5.9% -2.5, -9.4	0.37

Table 4.1.1 Sensitivity analysis of the effect of excluding women who developed gestational diabetes, preeclampsia, gestational hypertension or experienced preterm birth on the percentage change in uterine artery pulsatility index over the course of gestation by maternal BMI category, expressed as percentage drop of Doppler PI between scanning timepoints. CI; Confidence Interval. Model 1 adjusted for gestational age at all scanning timepoints. Model 2 adjusted for gestational age at all scanning timepoints, maternal BMI, systolic blood pressure at 12 weeks gestation, marital status, maternal age, maternal ethnicity, maternal smoking status and deprivation index. *p-value relative to mean uterine artery pulsatility index drop in normal weight women at same scanning timepoint.

4.5 Discussion

4.5.1 Main findings

We assessed the impact of maternal obesity and fetal sex on both utero-placental and feto-placental resistance over the course pregnancy, with the aim of improving understanding of the variability in risk of complications in successive pregnancies. We show that resistance in the utero-placental circulation is independently influenced by both maternal BMI and fetal sex. The physiological drop in uterine artery PI over the course of gestation was attenuated in women who were overweight or obese compared to women whose BMI was in the normal range. The impact of maternal BMI on utero-placental resistance became greater as the pregnancy progressed. By contrast, the impact of fetal sex on utero-placental resistance was consistent throughout gestation. Women carrying a male fetus had consistently higher uterine artery doppler PI compared to women carrying female fetuses at every measured time-point.

Resistance in the feto-placental circulation was independent of maternal BMI but influenced by fetal sex. Pulsatility index in the umbilical artery was higher in women carrying a female fetus compared to women carrying a male fetus at all time-points, but the magnitude of difference between sexes reduced with increasing gestation.

Previous studies have shown similar patterns when investigating fetal sex differences in the absolute values of UtA-PI in the second and third trimester [303], and between maternal prepregnancy BMI and higher UtA-PI in the third trimester [313]. However, in contrast to our study, prior research did not assess the physiological change in vascular resistance over the course of gestation or a possible interaction between maternal BMI and fetal sex.

4.5.2 Strengths and Limitations

A major strength of the current work is the detailed phenotyping and completeness of the data available regarding pregnancies in the POP cohort [267]. In particular, longitudinal ultrasonographic measurements of both the uterine and umbilical artery pulsatility indices from 20 weeks of pregnancy through to 36 weeks are available on a large cohort of nulliparous women. Moreover, the detailed set of covariates in the POP study dataset allowed adjustment of the models for other relevant maternal characteristics. A limitation of this study is the lack of availability of other Doppler parameters (e.g. resistance index) as well as the lack of longitudinal blood pressure data, as previous studies have shown a significant effect of

maternal weight [314, 315] as well as fetal sex [303] on the systolic and diastolic blood pressure.

4.5.3 Interpretation

Our study confirms the finding of previous research that the UtA-PI steadily declines over gestation [316, 317]. Up to halfway in pregnancy, this process is thought to reflect the conversion process of the spiral arteries [318]. Additionally, there are several possible explanations for the further reduction in resistance in the uterine artery in the second half of pregnancy [316]. Firstly, trophoblast invasion and further remodelling of the spiral arteries could continue in the second and third trimester. Secondly, the uterine artery will dilate throughout gestation, most likely induced by activation of nitric oxide synthase by estrogens and higher shear stress as a result of increased flow resulting from increased cardiac output [46]. Together with other maternal haemodynamic changes such as lower blood viscosity and reduced peripheral resistance this can lead to a reduction in vascular resistance in the uterine artery.

Obese women had higher absolute UtA-PI values at 20 wkGA compared to normal weight and overweight women, possibly reflecting poorer spiral artery remodelling up to that point in gestation [318]. Uterine natural killer cells, involved in the spiral artery remodelling process, exhibit functional changes in gene expression and growth factor signalling when exposed to maternal obesity [319] and could therefore restrict the adaptation process. Additionally, a previous study has found a 'dose-dependent' increase in the risk of abnormal spiral artery conversion with an increase maternal prepregnancy BMI [152].

Remodelling of the uterine vasculature is one of the major changes required to provide adequate utero-placental perfusion and subsequently facilitate fetal growth [320]. As mentioned above, poorer maternal haemodynamic adaptation to pregnancy in obese women could be underpinning the diminished drop in UtA-PI. For instance, obese women have a decrease in cardiac output in the third trimester [321]. Outside of pregnancy, flow-mediated vasodilation also seems reduced in brachial artery of obese women compared to lean women [322]. As mentioned above, in pregnancy, flow-mediated dilation of the uterine artery is mediated by the release of nitric oxide (NO) [46]. Moreover, endothelial-dependent vasodilation is significantly lower in obese women during pregnancy at each trimester compared to normal weight women [147]. There is an extensive literature suggesting that obesity impairs NO availability (reviewed in [323–325]), suggesting that reduced NO availability might play a

role in impaired (flow-mediated) vasodilation and subsequently higher UtA-PI values.

Few previous studies have examined differences in utero-placental vascular resistance by fetal sex. Widnes and colleagues reported no differences in uterine artery resistance at 22-24 weeks gestation between fetal sexes [304], whereas, Broere-Brown reported a systemically higher UtA-PI in the second and third trimester in women carrying a male fetus [303], consistent with the findings in this analysis. The mechanism by which fetal sex can influence pulsatility index in the uterine artery is not known, however, placental sex has a profound effect on the placental transcriptome, largely mediated by genes which escape from X chromosome inactivation. These differences include both previously recognised and placental-specific escapees and these changes in turn alter the maternal serum metabolome [282]. Hence, it is plausible that fetal sex may alter maternal cardiovascular adaptation to pregnancy [326]. However, there are also morphological differences in male versus fetal placentas, for example placental weight, capillary density and trophoblast differentiation [327, 328], which may be reflected in a direct difference in placental vascular resistance affecting flow in both the utero-placental and feto-placental circulations.

4.5.4 Conclusion

This analysis implies that higher BMI and male fetal sex are independent risk factors for higher resistance in the uterine artery, which act through distinct pathways. Previous reports suggest that there is a higher incidence of placenta-mediated pathologies, for example preeclampsia, in pregnancies with male rather than female fetuses [329], which could be linked to the observed differences in utero-placental and feto-placental blood flow. Furthermore, maternal prepregnancy BMI is also a known risk factor for pathologies linked to impaired utero-placental blood flow, for example FGR and preeclampsia [132, 330]. The finding that higher maternal BMI is associated with attenuation of the physiological drop in pulsatility index of the uterine artery across gestation provides impetus for further work exploring interventions that can improve utero-placental blood flow in mothers with higher BMI. Pulsatility index in the uterine artery is a key predictor of adverse pregnancy outcomes, such as preeclampsia and fetal growth restriction [287, 331], hence these findings give new insight into the independent risks posed by high maternal BMI and male fetal sex.

Chapter 5

Timing of gestational weight gain and the risk of developing preeclampsia or delivering a small for gestational age neonate; a prospective cohort study

The work in this chapter, including text and all figures, has been submitted to the British Journal of Obstetrics and Gynaecology for publication.

5.1 Chapter summary

Background: Gestational weight gain (GWG) is recognised to be a modifiable risk factor for adverse maternal and fetal perinatal outcomes. However, studies only assessing weight gain across the total gestational period might miss important gestational age-related differences in risk. Furthermore, although preeclampsia (PE) and small for gestational age (SGA) neonates share a background in placental dysfunction, studies suggest that higher weight gain is associated with a lower risk of SGA neonates, but a higher risk of developing PE. The aim of this study is therefore to investigate the association and timing of GWG on the risk of developing PE and delivering an SGA neonate.

Methods: Logistic regression quantified odds ratios for the associations between estimated weight gain per gestational age period (12-20 weeks of gestational age [wkGA], 20-28wkGA and 28-36wkGA) and preeclampsia (PE), SGA, or their combination.

Results: GWG at all gestational periods was associated with a lower risk of delivering an SGA neonate, and associations were stronger with earlier GWG (adjusted odds ratio (aOR) per 1 kg GWG 0.85 (95% confidence interval [CI] 0.80-0.91) at 12-20wkGA versus 0.94 (0.90-1.00) at 28-36wkGA, p -value for heterogeneity=0.02). Weight gain between 28 and 36wkGA was associated with a higher risk of developing PE (aOR 1.25; CI 1.18-1.33) and the risk of developing PE and having an SGA neonate simultaneously (aOR 1.18; CI 1.04-1.32). Associations were consistent across maternal pre-pregnancy body mass index categories.

Conclusion: GWG is differentially associated with the risk of developing PE and delivering an SGA neonate; the associations are in opposite directions and differ across gestation periods. Interventions targeted at second trimester weight gain may reduce the risk of SGA, without increasing the risk of PE.

5.2 Background

Gestational weight gain (GWG) is recognised to be a modifiable risk factor for adverse maternal and fetal perinatal outcomes and long-term cardio metabolic health in offspring [332]. Effects of total GWG across gestation are well studied [166, 333], exposing an association between excessive GWG (according to the National Academy of Medicine (NAM) criteria, previously known as the Institute of Medicine (IOM) guidelines) and common perinatal complications such as hypertensive disorders in pregnancy and delivering a large for gestational age neonate. However, studies only assessing weight gain across total gestation might miss important gestational age-related differences in risk. Moreover, weight gain in early pregnancy is thought to reflect maternal fat deposition, whereas later GWG can be attributed to growth of the fetus, placenta and uterus [334], possibly having differential effects on fetal and maternal outcomes. Furthermore, if patterns of GWG are better understood, they could be employed as monitoring tools for clinicians when interventions during gestation are still possible.

Preeclampsia (PE) and delivering a small for gestational age (SGA) neonate share a background of placental dysfunction, possibly based on an increase in oxidative stress [274, 278]. Maternal obesity is known to be associated with an increase in oxidative stress [335, 336], but less is known about the effects of GWG on the placental function. Previous studies suggest that excessive weight gain according to the NAM guidelines would be protective of delivering an SGA neonate, but is associated with a higher risk of developing PE. The association between timing of GWG and neonatal size has previously been studied [172, 337–339], but research on the association between trimester-specific weight gain on preeclampsia are sparse. To clarify the effects of the timing of GWG on these placental syndromes, we aimed to investigate the association and timing of GWG on the risk of developing PE, delivering an SGA neonate or these two complications combined (PE + SGA), using data from a prospective cohort of nulliparous women.

5.3 Methods

Women from the Pregnancy Outcome Prediction (POP) study were included in this analysis. The description of the POPS study design, inclusion criteria and general definitions can be found in Chapter 3.

5.3.1 Definitions specific for this analysis

All definitions used in this chapter can be found in **Chapter 3**.

5.3.2 Gestational weight gain

Gestational weight was measured at approximately 12, 20, 28 and 36 wkGA, with actual timing of visits ranging by average differences of around ± 4 days. Observed gestational weight was recalibrated to exactly 12, 20, 28 and 36 wkGA from a single linear regression of observed maternal weight on observed actual visit time, allowing for different intercepts and slopes for the four visits, and a random intercept for each mother to allow for dependency between repeated measures. Gestational weight gain in kg was then estimated for 12-20, 20-28, 28-36 and 12-36 wkGA, which was further classified as ‘adequate’, ‘inadequate’ and ‘excessive’, as per NAM guidelines [15]. Inadequate GWG was classified as weight gain less than 0.35, 0.28 or 0.22 kg/wkGA for normal, overweight and obese women, respectively. Excessive GWG was considered as weight gain more than 0.50, 0.33 or 0.27 kg/wkGA for normal, overweight and obese women, respectively.

5.3.3 Outcomes

Preeclampsia was defined as per 2013 classification of the American College of Obstetricians and Gynecologists (ACOG) [340]. Small for gestational age was defined as birthweight $<10^{th}$ centile, using fetal sex and gestational age adjusted reference standard derived from a UK population [341].

5.3.4 Statistical analysis

The predefined analysis plan for this study can be found in **Appendix 2**. In summary, a two-step modelling approach was used.

In the first step of the analysis, gestational weight gain for each women was corrected to an estimated weight gain for exactly 12-20, 20-28 28-36 and 12-36 wkGA using a mixed effect linear model to take into account the repeated measurements per woman. The model regressed weight on the difference in gestational age between the planned and the actual visit and the random intercept accounts for the dependency between measurements.

In the second step, separate ordinary logistic regression models were used to calculate odds ratios (ORs) for the associations between the new estimated weights from step 1 for each

gestation period (12-20, 20-28, 28-36 and 12-36wkGA) and (i) all PE (vs all non-PE, including SGA) (ii) all SGA (vs all non-SGA, including PE) and (iii) the combination of PE and SGA (vs all non-PE and non-SGA, including PE or SGA alone).

Effect modification by maternal body mass index (BMI) category was assessed using GWG and BMI interaction terms. Odds ratios (ORs) between gestation periods were formally compared using further single logistic models with GWG and gestation interaction terms and robust standard errors (to account for the dependencies of repeated measurements within each mother).

All models were fitted with and without adjustment for maternal BMI at 12 wkGA, maternal age, deprivation index, marital status, smoking status, maternal ethnicity and age at leaving fulltime education. All analyses were performed within R for windows, version 3.4.2. [310]

5.4 Results

5.4.1 Subject characteristics

A total of 4,512 women enrolled in the POP study, of whom 300 were lost to follow up. For this analysis, women with missing pre-pregnancy BMI ($n=7$), who were underweight ($n=68$, since this group was too small for interpretation) or with missing covariate information ($n=349$) were excluded (Figure 5.1). Of the remaining 3788 women, 2190 (57.8%) had a normal BMI, 1070 (28.2%) were overweight and 528 (13.9%) were obese. Estimated GWG was available for 3730 women between 12-20 wkGA, for 3623 women between 20-28 wkGA, for 3423 women between 28-36 wkGA and for 3468 women between 12-36 wkGA (Figure 5.1). GWG between 12-36 wkGA was lower in obese women than in normal weight women (Table 5.1). Women with higher prepregnancy BMI were more likely to be younger, smokers, and have pre-existing hypertension and diabetes (Table 5.1). The incidences of adverse outcomes in this cohort study were: all PE 6.6%, all SGA 8.9%, and PE + SGA simultaneously 0.7%.

5.4.2 Rate of weight gain in perinatal complications

The mean rate of GWG was 0.38 kg/week between 12-20 wkGA, 0.59 kg/week between 20-28 wkGA and 0.55 kg/week between 28-36 wkGA. Women who developed PE during pregnancy had a higher rate of GWG (in kg per week) between 28-36 wkGA compared to women without PE (0.72 kg/week vs. 0.53 kg/week respectively) (Figure 5.2). The rate

	Normal weight n=2190	Overweight n=1070	Obese n=528	Total n=3788
Maternal age (y)	30.0 (4.8)	30.4 (5.3)	29.4 (5.7)	30.0 (5.1)
Gestational age at visit (uncorrected)				
12 weeks	12.6 (0.8)	12.6 (0.8)	12.6 (0.9)	12.6 (0.9)
20 weeks	20.3 (0.5)	20.4 (0.5)	20.6 (0.5)	20.4 (0.5)
28 weeks	28.3 (0.4)	28.3 (0.4)	28.3 (0.4)	28.3 (0.4)
36 weeks	36.2 (0.4)	36.2 (0.4)	36.2 (0.4)	36.2 (0.4)
Ethnicity				
White	2048 (93.5%)	1016 (95.0%)	507 (96.0%)	3571 (94.3%)
Non-white	142 (6.5%)	54 (5.0%)	21 (4.0%)	217 (5.7%)
Deprivation score (quartile)				
1 (lowest)	562 (25.7%)	282 (26.4%)	113 (21.4%)	957 (25.3%)
2	535 (24.4%)	278 (26.0%)	129 (24.4%)	942 (24.9%)
3	546 (24.9%)	275 (25.7%)	133 (25.2%)	954 (25.2%)
4 (highest)	547 (25.0%)	235 (22.0%)	153 (29.0%)	935 (24.7%)
Smoking status				
Non-smoker	1405 (64.2%)	590 (55.1%)	266 (50.4%)	2261 (59.7%)
Quit pre-pregnancy	538 (24.6%)	341 (31.9%)	170 (32.2%)	1049 (27.7%)
Quit during pregnancy	5146 (6.7%)	94 (8.8%)	58 (11.0%)	298 (7.9%)
Current smokers	5101 (4.6%)	45 (4.2%)	34 (6.45%)	180 (4.8%)
Marital status				
(Married)	1553 (70.9%)	719 (67.2%)	324 (61.4%)	2596 (68.5%)
(Not married)	637 (29.1%)	351 (32.8%)	204 (38.6%)	1192 (31.5%)
Maternal weight (estimated, kg)				
12 weeks	60.9 (6.4)	73.4 (6.7)	92.0 (12.6)	68.8 (13.3)
20 weeks	64.1 (6.8)	76.5 (7.1)	94.2 (12.4)	71.8 (13.2)
28 weeks	68.8 (7.2)	81.4 (7.6)	98.4 (12.6)	76.5 (13.3)
36 weeks	73.2 (7.8)	86.2 (8.3)	102.5 (12.9)	80.8 (13.6))
Gestational weight gain ^a (estimated, kg)				
12-20 weeks	3.2 (2.1)	3.1 (2.6)	2.2 (2.4)	3.0 (2.3)
20-28 weeks	4.7 (4.7)	5.0 (2.3)	4.3 (2.2)	4.7 (2.2)
28-36 weeks	4.3 (2.3)	4.6 (2.4)	4.2 (2.7)	4.4 (2.3)
12-36 weeks	12.2 (3.7)	12.6 (4.5)	10.6 (5.3)	12.1 (4.2)
Pre-existing diabetes				
Yes	4 (0.2%)	10 (0.9%)	2 (0.4%)	16 (0.4%)
No	2186 (99.8%)	1060 (99.1%)	526 (99.6%)	3772 (99.6%)
Pre-existing hypertension				
Yes	63 (2.9%)	64 (6.0%)	68 (12.9%)	195 (5.1%)
No	2127 (97.1%)	1006 (94.0%)	460 (87.1%)	3593 (94.9%)
Preeclampsia				
Yes	91 (4.1%)	73 (6.7%)	85 (16.1%)	249 (6.6%)
No	2097 (95.8%)	996 (93.1%)	443 (83.9%)	3536 (93.3%)
Unknown	2 (0.1%)	1 (0.1%)	0 (0.0%)	3 (0.1%)
Small for gestational age				
Yes	218 (10.0%)	83 (7.8%)	38 (7.2%)	339 (8.9%)
No	1964 (89.7%)	975 (91.1%)	487 (92.2%)	3426 (90.4%)
Unknown	8 (0.4%)	12 (1.1%)	3 (0.6%)	23 (0.6%)
Birthweight (g)	3376 (516)	3430 (554)	3496 (575)	3408 (537)
Placental weight (g)	451 (96)	469 (107)	490 (112)	461 (102)

Table 5.1 Baseline and birth characteristics stratified by maternal BMI category. Data are represented as mean (SD) or as number (%). Differences in baseline characteristics were tested using chi-square tests and Kruskal-Wallis tests. ^aEstimated gestational weight available for 3730 women 12-20wkGA, 3623 women 20-28wkGA, 3423 women 28-36wkAG and 3468 women 12-36wkGA.

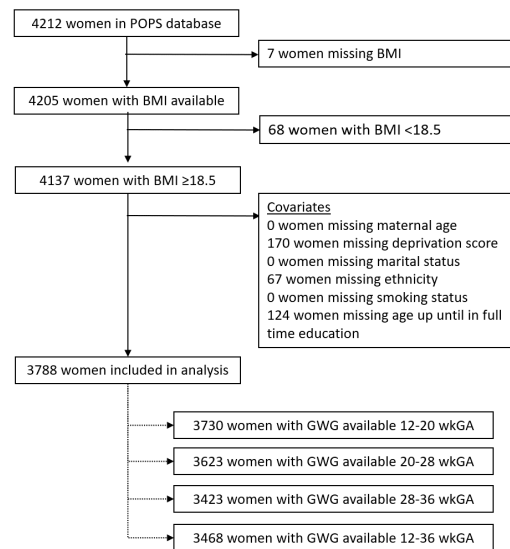


Fig. 5.1 Flow diagram showing in- and exclusion criteria. Amount of women that have information available on GWG decreased during gestation due to preterm birth and/or missed research appointments. 3766 women had at least one GWG measurement available. BMI; Body mass Index. GWG; gestational weight gain, wkGA; weeks gestational age.

of weight gain was lower for women who delivered an SGA neonate during all gestation periods compared to women delivering a non-SGA neonate (0.31 kg/week vs. 0.38 kg/week for 12-20 wkGA, 0.53 kg/week vs. 0.60 kg/week for 20-28 wkGA and 0.50 kg/week vs. 0.55 kg/week for 28-36 wkGA, respectively) (Figure 5.2). Women who developed PE and delivered an SGA neonate simultaneously had a higher rate of GWG between 28-36 wkGA compared to women who did not have these combined complications (0.54 kg/week vs. 0.73 kg/week, respectively) (Figure 5.2).

5.4.3 Timing of gestational weight gain per kg weight gain in relation to perinatal complications

Weight gain at any gestation period was associated with a lower risk of delivering an SGA neonate. The associations were strongest at 12-20 wkGA (adjusted odds ratio (aOR) per 1 kg GWG 0.85, 95% CI 0.80, 0.91), intermediate at 20-28wkGA (aOR 0.89 (0.85-0.94), $p=0.30$ for comparison with 12-20 wkGA) and weakest at 28-36wkGA (aOR 0.94 (0.90-1.00), $p=0.02$ for comparison with 12-20wkGA) (Figure 5.3. Weight gain between 28-36 wkGA was associated with a higher risk of developing PE (aOR 1.25 (1.18-1.33), $p<0.001$ for comparison with 12-20wkGA) (Table 5.2 and Figure 5.3). Weight gain between 28-36wkGA was also associated with a higher risk of developing PE and delivering an SGA neonate

simultaneously (aOR 1.18 (1.04-1.32), $p < 0.001$ for comparison with 12-20wkGA) (Figure 5.3). The associations for GWG were not modified by maternal BMI for any of the outcomes of interest, at any gestation period (Figure 5.4). Total GWG between 12-36 wkGA was also associated with a lower risk of delivering an SGA neonate (aOR 0.91 (0.89-0.94), Figure 5.3) and a higher risk of developing PE (aOR 1.10 (1.07-1.14), Figure 5.3). The associations did not change on adjustment for potential confounders (Table 5.2).

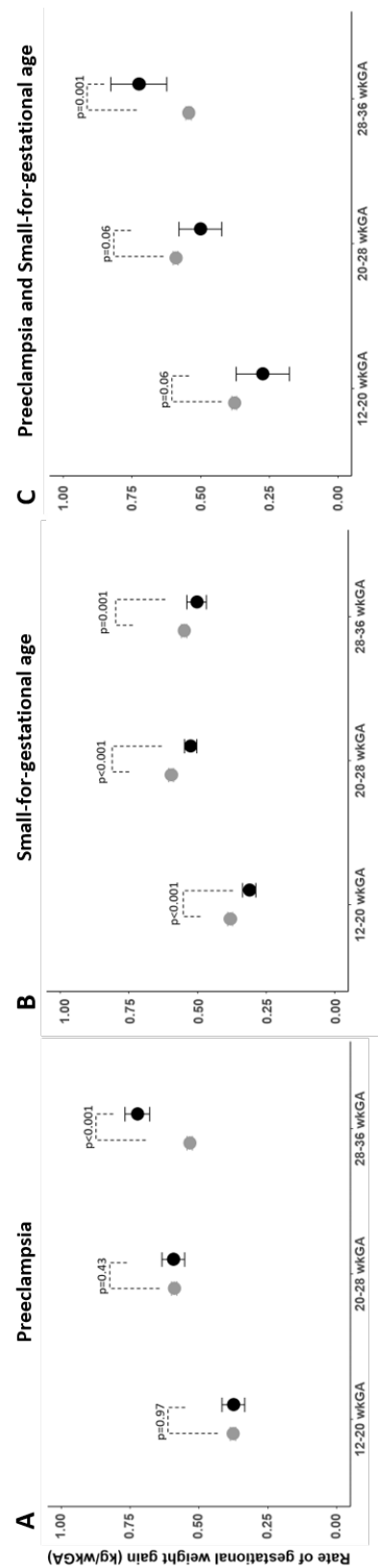


Fig. 5.2 Rate of gestational weight gain between women with and without perinatal complications. wkGA; weeks gestational age. A; Preeclampsia, B; Small for gestational age neonates, C; Preeclampsia and small for gestational age neonates simultaneously. Grey points and bars; women with previously mentioned complication, black points and bars; women with previously described complication. P-values are for difference between groups calculated using the two-sample Wilcoxon rank sum (Mann-Whitney) test for continuous variables.

5.4.4 Timing of gestational weight gain according to the NAM guidelines in relation to perinatal complications

Excessive weight gain between 12-36 wkGA, according to the NAM guidelines, was associated with a higher risk of developing PE (aOR 1.59 (1.14-2.23), Table 5.3). This appeared to be attributed to excessive late GWG between 28-36 wkGA (aOR 2.15 (1.36- 3.59)), with no associations at earlier gestation. In contrast, excessive weight gain between 12-20 wkGA and between 28-36 wkGA was associated with a lower risk of delivering an SGA neonate (aOR 0.72 (0.52- 0.99) and aOR 0.71 (0.53-0.96), respectively). There was no evidence of association between inadequate weight gain and the risk of developing PE although inadequate weight gain over the total course of gestation was associated with a higher risk of delivering an SGA neonate (aOR 1.83 (1.38- 2.43)). The associations did not change on adjustment for potential confounders (Table 5.3).

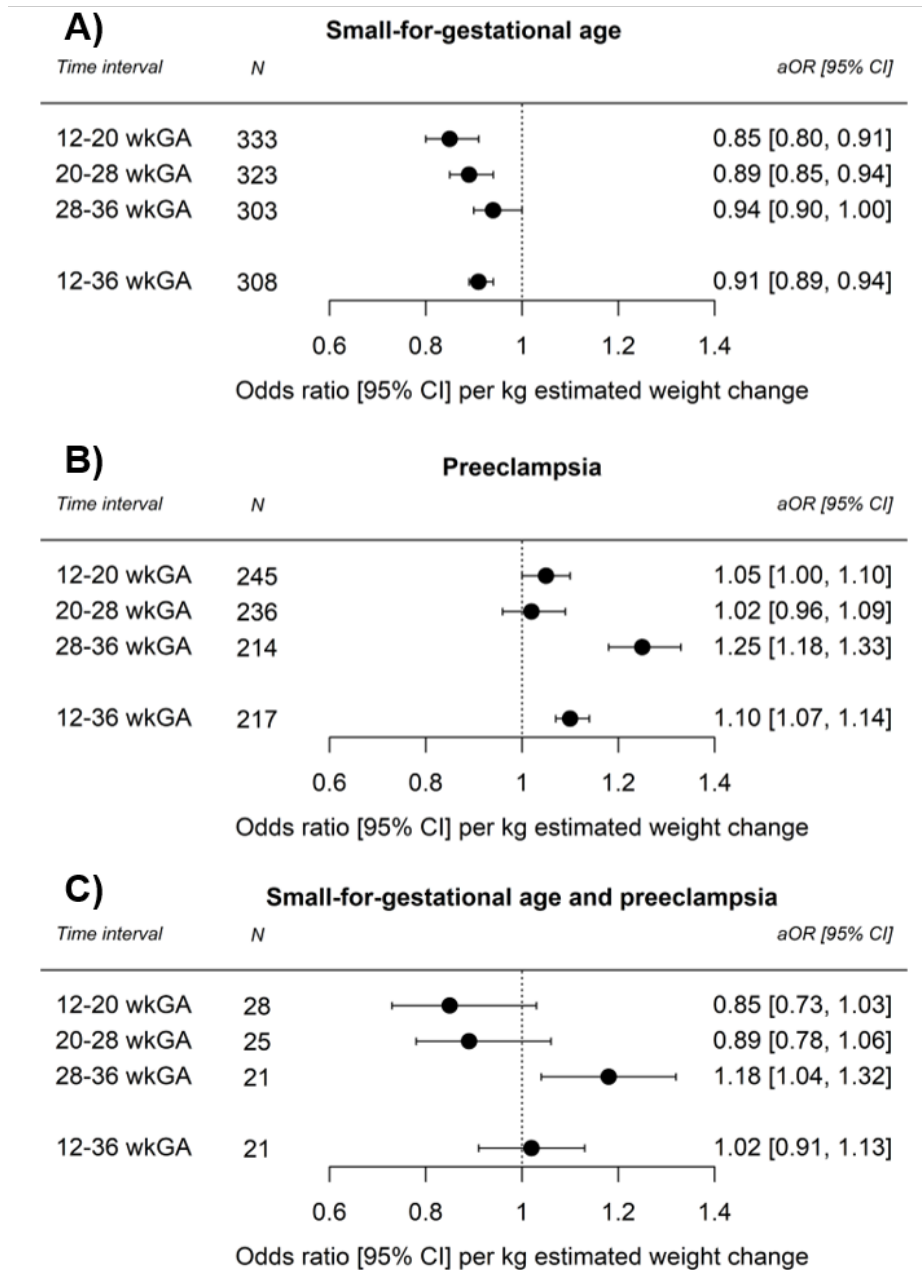


Fig. 5.3 Forest plot for the risk of delivering a (A) small for gestational age neonate (SGA), developing (B) preeclampsia (PE), or (C) SGA and PE simultaneously, stratified by timing of gestational weight gain. P-value for heterogeneity compared to 12-20wkGA time period: SGA 20-28wkGA: 0.30, 28-36wkGA $p=0.02$. PE 20-28wkGA $p=0.65$, 28-36wkGA $p<0.001$. PE + SGA 20-28wkGA $p=0.62$, 28-36wkGA $p<0.001$. aOR; adjusted odds ratio, CI; confidence interval, N; number of cases, wkGA; weeks gestational age.

	12-20 wkGA			20-28 wkGA			28-36 wkGA			12-36 wkGA		
	Unadjusted		Adjusted*	Unadjusted		Adjusted*	Unadjusted		Adjusted*	Unadjusted		Adjusted*
	N	OR (95% CI)	OR (95% CI)	N	OR (95% CI)	OR (95% CI)	N	OR (95% CI)	OR (95% CI)	N	OR (95% CI)	OR (95% CI)
Preeclampsia	245	1.00 (0.94-1.05)	1.05 (1.00-1.10)	245	1.01 (0.95-1.07)	1.02 (0.96-1.09)	214	1.28 (1.21-1.36)	1.25 (1.18-1.33)	217	1.09 (1.06-1.12)	1.10 (1.07-1.14)
Small for gestational age	333	0.88 (0.83-0.93)	0.85 (0.80-0.91)	333	0.89 (0.85-0.94)	0.89 (0.85-0.94)	303	0.94 (0.89-0.98)	0.94 (0.90-1.00)	308	0.92 (0.90-1.00)	0.91 (0.89-0.94)
Preeclampsia & Small for gestational age	28	0.84 (0.72-1.00)	0.85 (0.73-1.03)	28	0.89 (0.81-1.04)	0.89 (0.78-1.06)	21	1.17 (1.03-1.29)	1.18 (1.04-1.32)	21	1.01 (0.91-1.11)	1.02 (0.91-1.13)

Table 5.2 Timing of gestational weight gain and risk of perinatal complications. OR, odds ratio; CI, confidence interval. Odds ratios indicating the change in risk per kg estimated weight change in studied time period. Gestational weight gain was calculated as corrected maternal weight at later timepoint minus corrected maternal weight at earlier timepoint. Corrected weight was estimated as $Y^*_{ij} = Y_{ij} - b_j d_{ij}$ where b_j was estimated in mixed linear model, regressing maternal weight on the difference in gestational age between planned appointments and actual research appointments, with a random intercept for each mother. * Adjusted for maternal BMI at 12weeks gestation, maternal age, deprivation index, marital status, smoking status, maternal ethnicity, age at leaving fulltime education. Unadjusted group only contains women who had information available on all covariates used in the adjusted model.

	12-20 wkGA		20-28 wkGA		28-36 wkGA		12-36 wkGA	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Preeclampsia (n=249)								
Inadequate	0.93 (0.64-1.34)	0.73 (0.50-1.07)	1.49 (0.80-2.72)	1.14 (0.33-2.13)	0.73 (0.33-1.55)	0.57 (0.25-1.22)	0.55 (0.35-0.85)	0.61 (0.30-0.94)
Adequate	ref	ref	ref	ref	ref	ref	ref	ref
Excessive	1.43 (1.03-2.03)	1.07 (0.76-1.53)	1.56 (1.04-2.43)	1.14 (0.7-1.87)	3.11 (2.00-5.12)	2.15 (1.36-3.59)	2.26 (1.66-3.12)	0.61 (0.30-0.94)
Small for gestational age (n=339)								
Inadequate	1.33 (1.01-1.77)	1.40 (1.05-1.87)	1.23 (0.78-1.91)	1.20 (0.76-1.87)	1.03 (0.71-1.49)	1.04 (0.72-1.52)	1.89 (1.44-2.50)	1.83 (1.38-2.43)
Adequate	ref	ref	ref	ref	ref	ref	ref	ref
Excessive	0.68 (0.49-0.92)	0.72 (0.52-0.99)	0.78 (0.58-1.07)	0.81 (0.60-1.12)	0.64 (0.48-0.85)	0.71 (0.53-0.96)	0.91 (0.66-1.25)	1.00 (0.71-1.39)
Preeclampsia & Small for gestational age (n=28)								
Inadequate	2.05 (0.79-6.34)	1.61 (0.61-5.06)	1.48 (0.29-6.78)	1.36 (0.26-6.46)	Nil cases	Nil cases	0.57 (0.15-1.82)	0.54 (0.14-1.74)
Adequate	ref	ref	ref	ref	ref	ref	ref	ref
Excessive	0.92 (0.29-3.11)	0.67 (0.21-2.31)	0.92 (0.34-3.21)	0.80 (0.28-2.85)	6.41 (1.33-11.5)	6.46 (1.28-11.8)	1.24 (0.47-3.33)	1.12 (0.40-3.22)

Table 5.3 Timing of gestational weight gain and risk of perinatal complications of interest according to the IOM guidelines for gestational weight gain. OR, odds ratio; CI, confidence interval. Odds ratios indicating the change in risk for inadequate or excessive weight change, compared to women gaining adequate weight according to the IOM guidelines. Categories were calculated based on corrected weight gain, estimated as $Y_{ij}^* = Y_{ij} - b_j d_{ij}$ where b_j was estimated in mixed linear model, regressing maternal weight on the difference in gestational age between planned appointments and actual research appointments, with a random intercept for each mother. * Adjusted for maternal BMI at 12weeks gestation, maternal age, deprivation index, marital status, smoking status, maternal ethnicity, age at leaving fulltime education. Unadjusted group only contains women who had information available on all covariates used in the adjusted model.

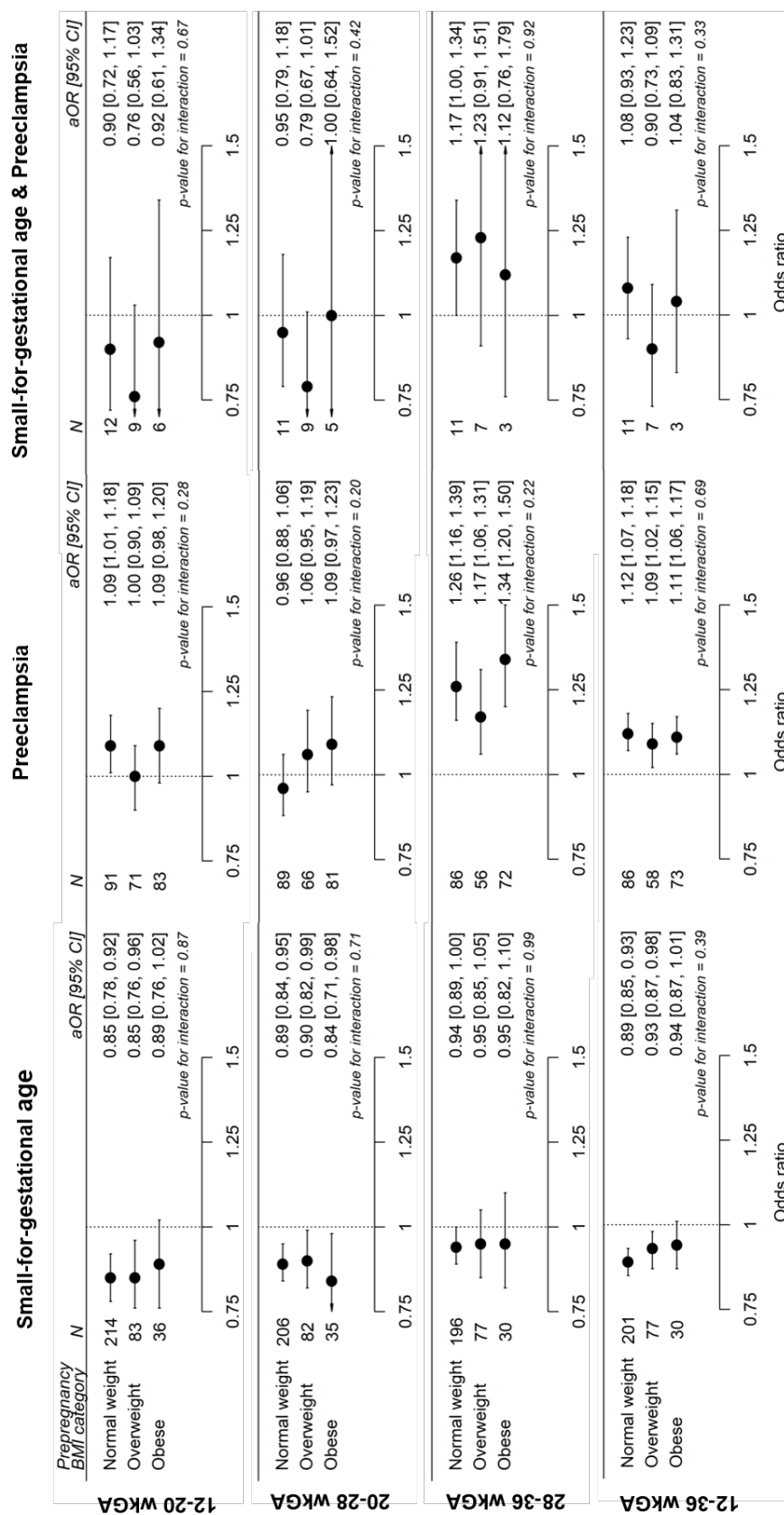


Fig. 5.4 Forest plot for the risk of delivering a small for gestational age (SGA) neonate, developing preeclampsia (PE), or SGA and PE simultaneously, stratified by maternal prepregnancy BMI category and timing of gestational weight gain. aOR; adjusted odds ratio, CI; confidence interval, N; number of cases, wkGA; weeks gestational age.

5.5 Discussion

5.5.1 Main findings

We assessed timing of weight gain during pregnancy on the risk of developing PE or SGA, two common perinatal complications, with the aim of understanding risk patterns across gestation. Our main findings suggest that weight gain during late gestation is associated with a higher risk of developing PE and weight gain at any gestation stage, but especially during earlier gestation, is associated with a lower risk of delivering an SGA neonate. These associations were consistent for GWG characterised as kg weight gained, when classified according to the NAM criteria, and across maternal prepregnancy BMI categories.

5.5.2 Strengths and limitations

Our study included only nulliparous women, thereby limiting the influence of parity on perinatal outcomes. To limit confounding, this study adjusted for a variety of risk factors. To correct for variation in observed timings of maternal weight measurements around planned visits, calibration methods which enabled accurate estimation of weight gain within pre-specified gestation periods were used, accounting for multiple measurements and allowing each woman's trajectory to vary about the population average [342]. Furthermore, it was possible to account for effect modification by maternal BMI, allowing for the estimation of effects of prepregnancy BMI.

Nevertheless, the study has some potential limitations. First, it was not possible to study weight gain in relation to PE up to time of diagnosis, due to unavailable data on time of diagnosis or repeated measurements of blood pressure (which would have enabled censored follow-up at the latest blood pressure within the normal range) [343]. The latest weight measurements were observed at around 36wkGA, which preceded the diagnosis of most PE. To further elucidate this, a sensitivity analysis was conducted separating PE in preterm and term diagnosis, by gestational age at delivery (preterm defined as delivery <37wkGA), which did not alter our results (data not shown). Second, SGA neonates are a heterogeneous group of neonates, including constitutionally small and pathologically small neonates. It is important to separate these groups, as truly growth restricted neonates are known to have worse outcomes. Although it is very difficult to properly distinguish these subgroups, a sub-analysis which divided SGA into SGA in the presence or absence of ultrasonic markers of growth restriction, based on a Delphi panel consensus of the diagnosis [101], did not alter the results (data not shown). Third, pre-pregnancy weight was not measured and therefore

it was not possible to assess the first trimester GWG. Fourth, the cohort were mostly white and from relatively affluent areas, and thus results may not generalise to other populations, although recent studies have shown weight gain patterns are similar across different local populations [344]. Fifth, the number of women affected by both complications (PE and SGA) simultaneously was too small to draw meaningful conclusions. Sixth, strict classification of GWG into the NAM categories places women with a wide range of weight gain in the same group. Method of GWG calculations (e.g. using preconception weight, first trimester weight and/or correction for gestational age) have a large influence on the category that women fall under [345]. However, the associations between GWG and outcome in the current study were consistent regardless whether GWG was classified according to the NAM criteria or characterised per 1 kg weight gained.

5.5.3 Interpretation

This study has highlighted the complex and diverse potential mechanisms by which weight gain may exert on perinatal outcomes. Both PE and fetal growth restriction (a subset of SGA) are associated with placental dysfunction and resistance patterns in the uterine and umbilical artery [346, 347], however, it is unclear why abnormal placental function in some cases leads to fetal growth restriction and other times to PE. The opposite associations with GWG may be a clue to divergence of the pathways leading to these conditions. The potential for divergent metabolic pathways was highlighted by the observation that maternal serum levels of the polyamine, N1,N12-diacetylspermine, were positively associated with preeclampsia but negatively associated with SGA [282]. Our study confirms the established observed association between GWG over the full course of pregnancy and the risk of developing PE [333], and strengthens emerging evidence that it is weight gain in later pregnancy which is most important [9, 175]. However, the direction of a possible causal mechanism remains unclear. Preeclamptic pregnancies are characterised by vascular permeability and subsequent oedema, which could explain rapid and excessive weight gain. This is supported by the observation that the difference in total GWG at 36 wkGA between women with and without PE was almost equal to the difference in total body water [164].

Weight gain during pregnancy is thought to include an increase in maternal fat mass, lean mass and body water, additionally to the increase in weight from fetal (derived) tissues. Few studies have focused on the relationship between patterns of GWG and changes in maternal body composition. Hence, little is known about the influence of these individual components on perinatal outcomes. Several studies have shown an association between second trimester weight gain and neonatal size [172, 173, 348, 170, 174, 349, 350]. More recently, a study

showed an association between the rate of GWG in the second trimester and greater maternal fat mass, which was subsequently associated with neonatal size [334]. However, Butte and colleagues showed an association between total maternal lean mass and a higher birthweight [351], but not between total maternal fat mass and birthweight. Clarifying these associations between separate components of GWG and birthweight could shed light on possible mechanisms by which GWG influences fetal growth and perinatal complications. Furthermore, early detection of excessive or inadequate gain of these elements may be predictive of future complications, e.g excessive water retention might precede a diagnosis of PE [352].

The opposite direction of associations between GWG and SGA and PE suggest that interventions to enhance weight gain might reduce the risk of SGA at the expense of increased risk of PE, if causality is assumed. A key finding of the present study is that the possible protective effect of GWG on SGA is most marked prior to 28wkGA and that there is no association between GWG and PE at this interval. These data indicate that if interventions to reduce the risk of SGA through increased weight gain are considered, they may be optimally targeted at the second trimester of pregnancy (12wkGA to 28wkGA). However, women typically demonstrate a wide range of weight gain during gestation. This complicates the design of an intervention to prevent the risk of SGA and questions clinical feasibility of such an intervention. A large meta-analysis investigating the effect of dietary- and exercise interventions in pregnancy on GWG and subsequent perinatal outcomes showed that dietary interventions can reduced total GWG, while simultaneously lowering the risk for preeclampsia without a higher risk of delivering an SGA neonate [353]. However, to my knowledge, no (randomised) trial has investigated the opposite; whether increased weight gain in early pregnancy can prevent SGA neonates, and what the effect on other perinatal outcomes is.

5.5.4 Conclusions

In conclusion, weight gain during late gestation is associated with a higher risk of developing PE, and weight gain especially during earlier gestation is associated with a lower risk of delivering an SGA neonate. The opposite direction of these associations suggests a mechanism influenced by GWG that diverges a pregnancy down the PE or SGA route, despite a shared pathophysiology in placental dysfunction. The associations at differential timings suggest the second trimester as an optimal target for weight interventions to reduce the risk of PE, without increasing the risk of SGA.

Chapter 6

Relationship between maternal prepregnancy body mass index and ultrasonic markers of fetal growth restriction in small for gestational age fetus; a prospective cohort study.

6.1 Chapter summary

Background: Maternal obesity is thought to be associated with a higher risk of delivering a pathologically small neonate as opposed to a constitutionally small neonate, due to suboptimal placental function. The aim of the current study is therefore to determine the association between maternal prepregnancy body mass index (BMI) and the risk of delivering a small for gestational age (SGA) neonate in the presence or absence of ultrasonic markers of fetal growth restriction (FGR).

Methods: The analysis included 3,633 nulliparous women that delivered >37 weeks gestation, from the Pregnancy Outcome Prediction study, a prospective cohort study conducted in Cambridge, UK, between 2008 and 2012. The women had fetal growth measurements available from serial ultrasonic scans. Fetal growth restriction classification was based on birthweight (BW) centile (population-based, corrected for fetal sex and gestational age) and components of a Delphi panel consensus for growth restriction. A multinomial regression model was used to quantify and formally compare the associations between maternal prepregnancy BMI (per one unit higher BMI and categorised as normal, overweight or obese) and the risk of delivering an SGA neonate in the presence (cases = 188) or absence (cases = 125) of ultrasonic FGR markers, with adjustment for confounders. Sensitivity analyses investigated different FGR definitions.

Results: Maternal prepregnancy BMI was similarly associated with a lower risk of delivering an SGA neonate in the presence of FGR markers (adjusted odds ratio (aOR) 0.96 [95% confidence interval (CI) 0.92-0.98], per one unit higher BMI), and a lower risk of delivering an SGA neonate in absence of FGR markers (aOR 0.95 [0.92-1.00]) (p-value for difference=0.70). Further, compared to women with a normal BMI, obese women had a lower risk of delivering an SGA neonate in the presence of FGR markers (aOR 0.54 [0.33-0.91]) and absence of FGR markers (aOR 0.76 [0.36-1.19] (p-value for difference = 0.65). Use of customised BW centiles attenuated the association between maternal prepregnancy BMI and the risk of delivering an SGA neonate in the presence or absence of FGR markers (aOR 1.00 [0.97-1.03] and aOR 1.04 [1.0-1.07], respectively). Different definitions of FGR did not materially change these associations.

Conclusion: Maternal prepregnancy BMI is similarly associated with a lower risk of delivering an SGA neonate in the presence or absence of ultrasonic markers of FGR at term. Obese women are not at higher risk of delivering a pathologically small neonate at term.

6.2 Background

The prevalence of obesity in pregnancy is rising worldwide. Maternal prepregnancy body mass index (BMI) and obesity are known to be associated with a higher risk of delivering a large for gestational age (LGA) neonate [333]. However, there are conflicting results with regards to maternal obesity and the risk of delivering a small for gestational age (SGA) neonate [333, 118].

Many studies use definitions of SGA and fetal growth restriction (FGR) interchangeably, though SGA neonates are a heterogeneous group that can be divided in constitutionally small or pathologically growth restricted fetuses. Distinguishing these two forms of SGA is important, as fetuses affected by FGR have a higher risk of perinatal morbidity [354] and mortality [99], as well as a higher risk of long term adverse consequences on cardiovascular [355, 356] and neurodevelopmental health [357]. It is hypothesised that obese women have a higher risk of delivering a pathologically rather than a physiologically small baby, as they are thought to have suboptimal placental function that in turn could impair fetal growth, possibly due to increased inflammation and impaired spiral artery remodelling[358, 359, 319]. Furthermore, SGA neonates born to obese women have poorer perinatal outcomes compared to SGA neonates born to normal weight women[360].

Limiting factors for research into FGR are the numerous definitions used, as well as the lack of longitudinal ultrasound data. In 2015, a Delphi panel was conducted to aim for consensus of the definition and to aid research into FGR. The consensus definition reached is based on biometric as well as functional parameters [101]. The Pregnancy Outcomes Prediction (POP) study had the unique opportunity to gather longitudinal ultrasonic measurements on fetal growth and uteroplacental Dopplers, while clinicians and patients were blinded to the results of the research scans. This allowed for distinction between healthy but small neonates or pathologically small neonates, based on the Delphi panel consensus.

Therefore, the aim of the current study was to determine the association between maternal prepregnancy BMI and the risk of delivering an SGA infant, where SGA was sub-grouped by the presence or absence of ultrasonic markers of FGR.

6.3 Methods

Women from the Pregnancy Outcome Prediction (POP) study were included in this analysis. The description of the POP study design, inclusion criteria and general definitions can be found in **Chapter 3**.

6.3.1 Definitions specific for this analysis

All definitions used in this chapter can be found in **Chapter 3**.

6.3.2 Outcomes

The primary outcome was SGA neonates born ≥ 37 wkGA, in the presence or absence of ultrasonic markers of FGR. Small for gestational age was classified as birthweight $< 10^{th}$ centile using a fetal sex and gestational age adjusted reference standard based on the UK population [341]. Fetal growth restriction was defined as either (A) birthweight $< 3^{rd}$ centile based on the UK population standard or (B) birthweight $< 10^{th}$ centile and at least one of the following two criteria (i) slow growth velocity, defined as abdominal circumference crossing > 2 quartiles from 20 wkGA visit to 36 wkGA visit or from 28 wkGA visit to 36 wkGA visit (equivalent to a change in z score of less than -1.35 in the POP study) (ii) pulsatility index of the umbilical artery $> 95^{th}$ percentile at 36 wkGA using Acharya reference [361]. This definition of FGR is based on a Delphi panel consensus [101]. The reference group was neonates born at a non-SGA weight (defined as birthweight $\geq 10^{th}$ centile) regardless of the presence or absence of ultrasonic markers of FGR. To further investigate the components of the FGR definitions, we used a previously defined [104] abdominal circumference growth velocity (ACGV), a difference between the exact gestational age-adjusted z scores in abdominal circumferences measured at 20 and 36 wkGA.

6.3.3 Exposure and confounder definitions

Maternal weight at booking scan (~ 12 wkGA) was used as a proxy for prepregnancy weight. BMI was calculated from maternal prepregnancy weight and maternal height. Maternal BMI categories are based on the World Health Organisation categories, with BMI ≤ 24.9 kg/m² as normal weight, 25-29.9 kg/m² as overweight and ≥ 30 kg/m² classified as obese. Covariates were selected based on clinical relevance. Maternal age was defined as age at recruitment. Age at leaving full time education (as a proxy for social-economic status) and ethnicity were self-reported by questionnaire at the 20 wkGA scan. Gestational age was based on ultrasonic

estimation at first scan. Deprivation score was based on the Index of Multiple Deprivation 2007 [269], which is based on census data from the area of the mother's postcode.

6.3.4 Data analysis

The predefined analysis plan for this study can be found in **Appendix 3**. In summary, differences in baseline characteristics were compared using chi-square tests and Kruskal-Wallis test, where appropriate. As the SGA outcome has multiple levels (non-SGA, SGA in the presence of ultrasonic FGR makers and SGA in the absence of ultrasonic FGR makers), multinomial regression analyses rather than a simple logistic regression model were used to quantify odds ratios for the associations between maternal prepregnancy BMI and the risk of delivering an SGA neonate in the presence of ultrasonic FGR markers, or an SGA neonate in the absence of FGR markers. The non-SGA group was set as the comparison level. For the outcome 'All SGA' a simple logistic regression analysis was used to quantify the association between maternal prepregnancy BMI and any SGA (i.e. in presence or absence of ultrasonic FGR markers).

Adjustment was made for maternal systolic blood pressure measured at 12 weeks, maternal ethnicity, maternal age, marital status, maternal smoking status and deprivation index. The differences in odds ratios were formally assessed using a Wald test.

To investigate the association between maternal prepregnancy BMI and ACGV, odds ratios from logistic models were used to quantify the associations between BMI categories and lowest or highest decile of ACGV, and regression coefficients from a linear model were used to quantify the associations between BMI categories and the ACGV z-score. The reference group for women with ACGV in the lowest decile (D1) were women with an ACGV in D2-D10, the reference group for women in the highest ACGV decile (D10) were women with an ACGV in D1-D9.

As sensitivity analyses, we repeated the analyses using customised birthweight centiles to define SGA (based on the Bulk calculator GROW, version 6.7.8.1, from the Perinatal institute, Birmingham, UK), excluded LGA neonates (BW >90th centile) from the control group, utilised SGA plus complications (defined as perinatal mortality, morbidity or preeclampsia) as outcome, as well as SGA plus low Placenta Growth Factor (PIGF) levels (defined as lowest decile (D1) of GA and maternal weight corrected MoM of PIGF concentration within the POP Study cohort versus D2-D10).

All odds ratios for overweight and obese women are relative to normal weight women, unless otherwise stated. Statistical analyses were preformed using R, version 3.4.2. [310].

6.4 Results

6.4.1 Subject Characteristics

The POP Study recruited 4,512 women, of whom 4,212 remained in the study and were followed through to delivery (most of the 300 women lost to follow up ended up delivering elsewhere). For this analysis, the following were excluded: women with missing information on BMI (n=7), women with stillbirth or miscarriage (n=45), women who delivered before 37 weeks gestational age (wkGA) (n=179), as most of them would not have attended the 36 wkGA research appointment and women with missing information on potential confounders (n=348, Figure 6.1). Of the remaining 3,633 women, 188 (5.1%) delivered an SGA neonate in the presence of ultrasonic FGR markers and 125 (3.4%) delivered an SGA neonate in the absence of FGR makers (Table 6.1). Women delivering an SGA neonate in the presence of FGR markers were more likely to be current smokers and be of white ethnicity than women delivering an SGA neonate in the absence of FGR markers. Neonates born SGA had a lower birthweight than neonates not born SGA, as well as a lower placental weight (Table 6.1).

6.4.2 Maternal prepregnancy BMI and the risk of an SGA neonate in presence or absence of FGR markers

Maternal prepregnancy weight was associated with a lower risk of delivering an SGA neonate (adjusted odds ratio (aOR) 0.95 [95% confidence interval (CI) 0.93-0.98], per one-unit higher prepregnancy BMI) (Table 6.2). When SGA was sub-divided by the presence or absence of ultrasonic markers of FGR, maternal prepregnancy BMI was similarly associated with a lower risk of delivering an SGA neonate in the presence of FGR markers (aOR 0.96 [0.92-0.98]) (Table 6.2), and of delivering an SGA neonate in the absence of FGR makers (aOR 0.95 [0.92-1.00]). There was no evidence of a difference in these odds ratios (p=0.70). The associations did not change on adjustment for confounders.

Obese women had a lower risk of delivering an SGA neonate in the presence or absence of FGR markers (aOR 0.54 [0.33-0.91] and aOR 0.76 [0.36-1.19], respectively, p-value for difference = 0.65) (Table 6.2). An overweight BMI was not associated with the risk of

delivering an SGA neonate in the presence (aOR 0.76 [0.53-1.07]) or absence of ultrasonic FGR markers (aOR 0.80 [0.52-1.23]) (p-value for difference = 0.83) (Table 6.2). These associations did not change on adjustment for confounders.

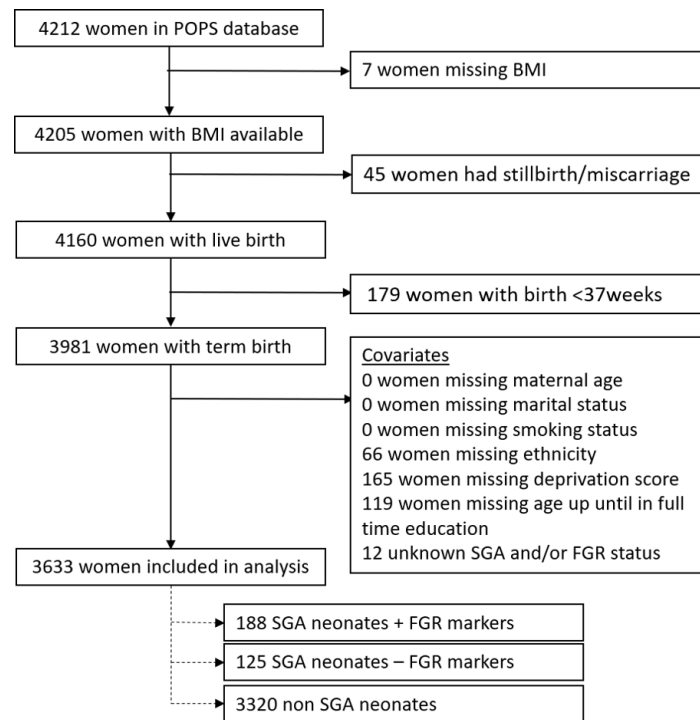


Fig. 6.1 Flow diagram for studying the relationship between maternal BMI and the presence or absence of ultrasonic markers of fetal growth restriction in fetuses born small for gestational age. BMI; Body Mass Index, FGR; fetal growth restriction, POPS; Pregnancy Outcome Prediction Study, SGA; small for gestational age.

6.4.3 Maternal prepregnancy BMI and fetal abdominal circumference growth velocity

The risk of experiencing an abdominal circumference growth velocity (ACGV) in the lowest decile (irrespective of eventual birth weight) was about 40% lower for overweight and obese women (aOR 0.62 [0.47-0.88] and aOR 0.56 [0.38-0.80], respectively) (Figure 6.2). In contrast, the risk of having an ACGV in the highest decile was about 50-80% higher for overweight and obese women (aOR 1.79 [1.40-2.29] and aOR 1.52 [1.10-2.11], respectively). These correspond to about 0.1-0.2 standard deviation higher ACGV z-score amongst overweight and obese women.

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	Non-SGA (n=3320)	SGA in absence of FGR markers (n=125)	SGA in presence of FGR markers (n=188)	p-value for differences	Overall baseline characteristics (n=3633)
Maternal age (y)	30.0 (5.1)	30.2 (5.4)	30.1 (5.1)	0.51	30.0 (5.1)
Maternal BMI (kg/m ²)				0.15	
<25	1935 (5.3)	81 (64.8)	123 (65.4)		2139 (58.9)
25-29.9	916 (27.8)	31 (24.8)	47 (25.0)		994 (27.4)
>30	469 (14.1)	13 (10.4)	18 (9.6)		500 (13.8)
Ethnicity				0.03	
White	3137 (94.5)	111 (88.8)	176 (93.6)		3424 (94.2)
Non-white	183 (5.5)	14 (11.2)	12 (6.4)		209 (5.8)
Smoking status				<0.001	
Non-smoker	2003 (60.3)	78 (62.4)	97 (51.6)		2178 (60.0)
Quit pre-pregnancy	921 (27.7)	32 (25.6)	53 (28.2)		1006 (27.7)
Quit during pregnancy	260 (7.8)	10 (8.0)	11 (5.9)		281 (7.7)
Current smokers	136 (4.1)	5 (4.0)	27 (14.4)		168 (4.6)
Deprivation quartile				0.13	
(lowest) 1	841 (25.3)	30 (24.0)	49 (26.1)		920 (25.3)
2	839 (25.3)	27 (21.6)	40 (21.3)		906 (24.9)
3	827 (24.9)	24 (19.2)	53 (28.2)		904 (24.9)
(highest) 4	813 (24.5)	44 (35.2)	46 (24.5)		903 (24.9)
Married				0.20	
Yes	2271 (68.4)	77 (61.6)	123 (65.4)		2471 (68.0)
No	1049 (31.6)	48 (38.4)	65 (34.6)		1162 (32.0)
Preexisting DM				0.72	
Yes	11 (0.3)	0 (0.0)	1 (0.5)		12 (0.3)
No	3309 (99.7)	125 (100.0)	187 (99.5)		3621 (99.7)
Essential hypertension				0.54	
Yes	165 (5.0)	6 (4.8)	6 (3.2)		177 (4.9)
No	3155 (95.0)	119 (95.2)	182 (96.8)		3456 (95.1)
Preeclampsia				0.73	
Yes	202 (6.1)	7 (5.6)	14 (7.4)		223 (6.1)
No	3116 (93.9)	117 (93.6)	174 (92.6)		3407 (93.8)
Unknown	2 (0.1)	1 (0.8)	0 (0.0)		3 (0.1)
Pregnancy Induced Hypertension				0.61	
Yes	56 (1.7)	2 (1.6)	5 (2.7)		63 (1.7)
No	3262 (98.3)	122 (97.6)	183 (97.3)		3567 (98.2)
Unknown	2 (0.1)	1 (0.8)	0 (0.0)		3 (0.1)
Gestational Diabetes				0.11	
Yes	155 (4.7)	1 (0.8)	7 (3.7)		163 (4.5)
No	3160 (95.2)	124 (99.2)	181 (96.3)		3464 (95.3)
Unknown	5 (0.2)	0 (0.0)	0 (0.0)		5 (0.1)
Birthweight (g)	3526 (418)	2923 (204)	2708 (297)	<0.001	3463 (457)
Placental weight*(g)	474 (95)	380 (63)	372 (72)	<0.001	466 (97)

Table 6.1 Baseline and birth characteristics stratified by small for gestational age status. Data are presented as mean (standard deviation) or as number (%). Differences in baseline characteristics were tested using chi-square tests and Kruskal-Wallis tests, as appropriate. BMI; Body Mass Index, DM; diabetes mellitus, FGR; fetal growth restriction, SD; standard deviation, SGA; small for gestational age. *Placental weight was available for a sub-sample and the numbers were 3,057, 117 and 166, respectively.

6.4.4 Sensitivity analyses

Where customised birthweight centiles were used to classify SGA neonates, maternal prepregnancy weight was associated with a higher risk of delivering an SGA neonate in the presence of ultrasonic FGR markers (aOR 1.04 [1.00-1.07], per one unit higher prepregnancy BMI) and not associated with the risk of delivering an SGA neonate in the absence of FGR markers (aOR 1.00 [0.97-1.03]) (p-value for difference = 0.07) (Table 6.3). The associations did not change on adjustment for confounders.

Removing LGA neonates from the reference group did not change the associations between maternal prepregnancy weight and the risk of an SGA neonate in the presence or absence of FGR makers (aOR 0.96 [0.92-0.99] and aOR 0.95 [0.92-1.01] respectively) (p-value for difference = 0.70) (Table 6.3). The associations did not change on adjustment for confounders.

There was no evidence of associations between maternal BMI and severe SGA (classified as birthweight <3rd centile) (aOR 0.99 [0.94-1.04]), SGA plus perinatal morbidity (aOR 0.97 [0.91-1.03]) or SGA plus low PIGF (aOR 0.96 [0.90-1.02]) (Table 6.4). The associations did not change on adjustment for confounders.

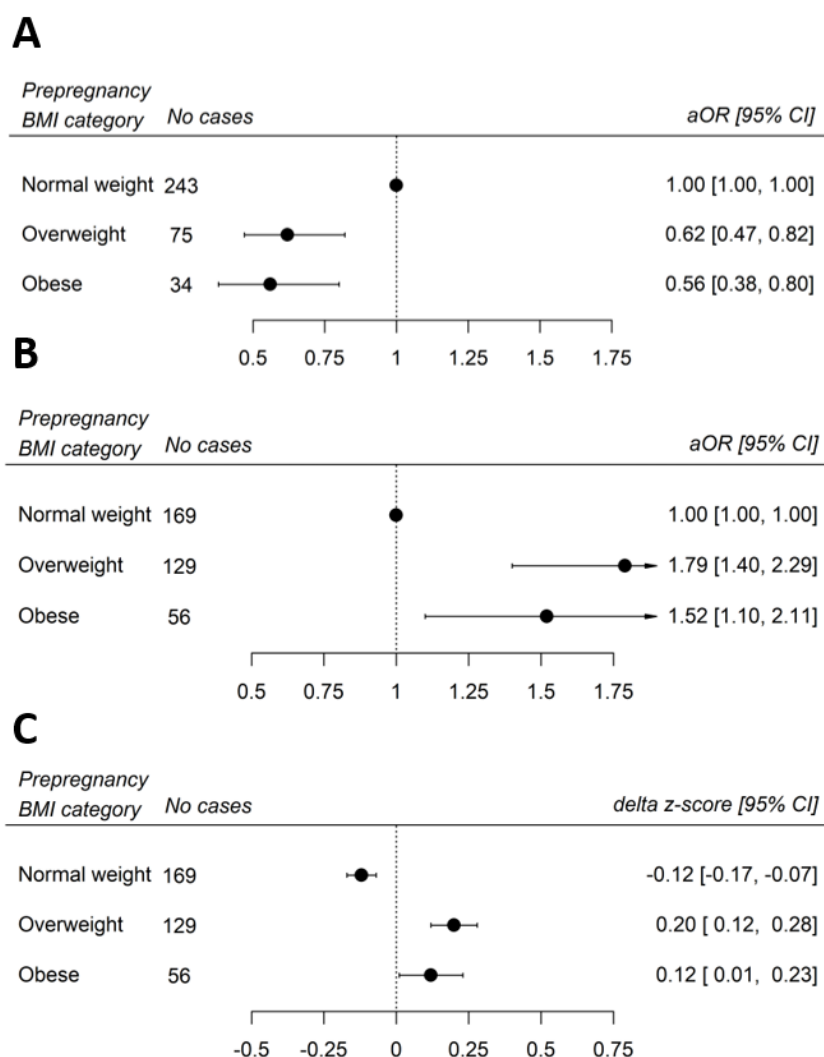


Fig. 6.2 Forest plots for the risk of carrying a fetus with abdominal circumference growth velocity (ACGV) between 20- and 36 weeks gestational age in (A) lowest decile or (B) the highest decile stratified by maternal prepregnancy BMI category. (C) Forest plot for change in ACGV z-score between 20-36 weeks gestational age stratified by maternal prepregnancy BMI category. BMI; Body Mass Index, CI; Confidence Interval.

	Unadjusted models					Adjusted models				
	Multinomial model			Logistic model		Multinomial model			Logistic model	
	SGA in presence of FGR markers (no cases=188)	OR (95% CI)	p-value	SGA in absence of FGR marker (no cases=125)	OR (95% CI)	p-value	SGA in presence of FGR markers (no cases=188)	OR (95% CI)	SGA in absence of FGR marker (no cases=125)	All SGA (no cases=313)
Prepregnancy BMI ^a	0.96 (0.92-0.99)	0.02	0.96 (0.92-1.00)	0.06	0.91	0.003	0.96 (0.93-0.99)	0.96 (0.92-0.98)	0.95 (0.92-1.00)	0.95 (0.93-0.98)
BMI categories ^b										
Normal weight	1.00 (ref)	-	1.00 (ref)	-	-	-	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Overweight	0.80 (0.57-1.13)	0.22	0.80 (0.53-1.22)	0.32	>0.99	0.11	0.80 (0.61-1.05)	0.76 (0.53-1.07)	0.80 (0.52-1.23)	0.77 (0.58-1.01)
Obese	0.60 (0.36-1.00)	0.05	0.66 (0.36-1.20)	0.17	0.81	0.02	0.63 (0.42-0.91)	0.54 (0.33-0.91)	0.76 (0.36-1.19)	0.59 (0.39-0.86)

Table 6.2 Association between maternal prepregnancy body mass index and the risk of delivering a small for gestational age neonate in presence or absence of ultrasonomic markers of fetal growth restriction. Odds ratios and 95% Confidence Intervals shown for risk of delivering a small for gestational age neonate with or without markers of fetal growth. ^aPer one-unit higher BMI, control group exists of all non-SGA neonates (n=3320). ^bCompared to the normal weight reference category. Adjusted models were corrected for maternal age, marital status, smoking status, maternal ethnicity, deprivation score and age at leaving fulltime education. BMI; Body Mass Index, CI; confidence interval, FGR; fetal growth restriction, OR; odds ratio, Ref; reference group, SGA; small for gestational age.

	Unadjusted models					Adjusted models						
	Multinomial model			Logistic model		Multinomial model			Logistic model		Logistic model	
	SGA in absence of FGR markers (no cases=188)	SGA in presence of FGR marker (no cases=125)	OR (95% CI)	p-value	p-value for difference	SGA in absence of FGR markers (no cases=188)	SGA in presence of FGR marker (no cases=125)	OR (95% CI)	p-value	p-value for difference	OR (95% CI)	p-value
Customised BW centiles ^a	1.01 (0.98-1.04)	0.51	1.04 (1.01-1.08)	0.01	0.13	1.03 (1.00-1.05)	0.03	1.00 (0.97-1.03)	0.89	1.04 (1.00-1.07)	1.02 (0.99-1.04)	0.17
Exclusion of LGA neonates ^b	0.96 (0.93-1.00)	0.03	0.96 (0.92-1.01)	0.10	0.91	0.96 (0.94-0.99)	0.008	0.96 (0.92-0.99)	0.01	0.95 (0.92-1.01)	0.96 (0.93-0.99)	0.003
Customised BW centiles & exclusion of LGA neonates ^c	1.01 (0.98-1.04)	0.40	1.05 (1.01-1.08)	0.007	0.13	1.03 (1.01-1.05)	0.008	1.00 (0.97-1.03)	0.94	1.04 (1.01-1.08)	1.02 (1.00-1.05)	0.07

Table 6.3 Association between maternal prepregnancy body mass index and the risk of delivering a small for gestational age neonate, divided by alternative classifications and/or reference group. Odds ratios and 95% Confidence Intervals shown for risk of delivering a small for gestational age neonate with or without markers of fetal growth per one-unit higher BMI. ^aSGA diagnosis based on customised birthweight centiles; control group n=3292, SGA with markers of FGR n=211, SGA with markers of FGR n=127. ^bSGA diagnosis based on Delphi panel with exclusion of large for gestational age neonates; control group n=3,147, SGA with markers of FGR n=188, SGA with markers of FGR n=125. ^cSGA diagnosis based on Delphi panel criteria with exclusion of large for gestational age neonates; control group n= 3,030, SGA with markers of FGR n=211, SGA with markers of FGR n=127. Adjusted models were corrected for maternal age, marital status, smoking status, maternal ethnicity, deprivation score and age at leaving fulltime education. BW; birthweight, CI; confidence interval, LGA; large for gestational age, OR; odds ratio, FGR; fetal growth restriction, SGA; small for gestational age.

		No cases	Unadjusted Model		Adjusted Model	
			OR (95%CI)	p-value	OR (95%CI)	p-value
(i) SGA defined as BW <3 rd percentile						
	Prepregnancy BMI*	75	1.00 (0.95-1.05)	0.94	0.99 (0.94-1.04)	0.71
	BMI categories					
	Normal weight	49	1.00 (ref)	-	1.00 (ref)	-
	Overweight	16	0.69 (0.38-1.19)	0.20	0.63 (0.35-1.11)	0.12
	Obese	10	0.87 (0.41-1.65)	0.69	0.74 (0.35-1.43)	0.40
(ii) SGA plus perinatal complications*						
	Prepregnancy BMI*	56	0.98 (0.93-1.04)	0.60	0.97 (0.91-1.03)	0.37
	BMI categories					
	Normal weight	37	1.00 (ref)	-	1.00 (ref)	-
	Overweight	13	0.74 (0.37-1.35)	0.34	0.64 (0.33-1.20)	0.18
	Obese	6	0.67 (0.25-1.48)	0.36	0.57 (0.21-1.27)	0.21
(iii) SGA plus lowest decile of PIGF*						
	Prepregnancy BMI*	58	0.97 (0.91-1.02)	0.27	0.96 (0.90-1.02)	0.24
	BMI categories					
	Normal weight	36	1.00 (ref)	-	1.00 (ref)	-
	Overweight	18	1.05 (0.57-1.83)	0.87	1.00 (0.55-1.76)	0.99
	Obese	4	0.45 (0.14-1.15)	0.14	0.45 (0.13-1.14)	0.13

Table 6.4 Association between prepregnancy body mass index and composite outcomes of small for gestational age neonates. Odds ratios and 95% Confidence Intervals shown for the risk of (i) delivering a severely small for gestational age neonate (defined as BW<3rd percentile relative to population cohort) (ii) small for gestational age neonate with perinatal morbidity (defined as defined as perinatal mortality, morbidity or preeclampsia) (iii) small for gestational age plus lowest decile of PLGF levels (defined as lowest decile of gestational age and maternal weight corrected mean of median of PIGF concentration within the POP study). *Odds ratio per one-unit higher prepregnancy BMI. Control group for shown analyses consisted of all non-SGA neonates (n=3,320). Adjusted models were corrected for maternal age, marital status, smoking status, maternal ethnicity, deprivation score and age at leaving fulltime education. BW; birthweight, CI; confidence interval, OR odds ratio, PIGF; placenta growth factor

6.5 Discussion

6.5.1 Main findings

In this study, the relationship between maternal prepregnancy BMI and the risk of FGR was investigated. Consistent with many previous studies [333, 362], it was found that obese women were less likely to deliver an SGA infant. However, higher prepregnancy BMI was found to be similarly associated with a lower risk of delivering an SGA neonate irrespective of the presence or absence of ultrasonic markers of FGR. These associations were similar regardless of the FGR classification.

6.5.2 Strengths and limitations

The main strength of this study was that clinicians were blinded to the results of the ultrasonic assessment of fetal growth and hence did not interfere based on these results of the biometry scans. We had longitudinal data available on all biometric and functional parameters that were needed to diagnose FGR according to the Delphi panel consensus. We additionally tested other definitions of FGR (e.g. birthweight $<3^{rd}$ centile or based on biochemical markers). Furthermore, the detailed set of covariates that were available allowed for correction of relevant maternal characteristics. Nevertheless, this study had several limitations. The study was confined to nulliparous women, who are known to have higher risks of delivering an SGA neonate than parous women [283]. Additionally, the women in the POP study were mostly of white ethnicity and from affluent areas, but it is known that there are differences in SGA incidence and fetal growth velocity between ethnicities [363, 364].

6.5.3 Interpretation

Fetal growth restriction is known to be associated both with perinatal complications in the short term [99], and with poorer developmental outcomes in the child [355–357]. Though SGA neonates born to obese mothers have a higher risk of perinatal morbidity and mortality than SGA neonates born to women of healthy weight [360], these results indicate that this is not explained by a greater proportion of these SGA neonates being affected by FGR.

Fetal growth restriction is thought to originate from poor placentation and impaired (cardio-vascular) adaptation to pregnancy [362]. Recently, Tay and colleagues have shown that the uterine artery Doppler change is abnormally elevated in pregnancies affected by FGR [365]. Furthermore, as shown in **Chapter 4**, the physiological drop in the uterine artery pulsatility index is impaired in obese women [366]. Although these studies together suggest that

maternal obesity could be associated with impaired adaptation to pregnancy and subsequent FGR, the current study shows no higher risk of delivering an SGA neonate in the presence of ultrasonic FGR markers in obese women. There could be multiple reasons for the lack of association; (i) the impaired adaptation to pregnancy might not be severe enough to induce sufficient growth restriction or (ii) mechanisms other than impaired cardiovascular adaptation play a greater role in the development of FGR. Additionally, 'overnutrition' of the fetus in obese women [367, 368] could mask a possible association too, as growth restricted fetuses might not drop their birthweight <10th centile.

The overnutrition hypothesis suggests that high maternal plasma concentrations of glucose and free fatty acids permanently change neuroendocrine function and energy metabolism in the fetus during development which can consequentially lead to obesity in the (later life of) offspring [369, 368]. As prepregnancy BMI is positively correlated with glucose tolerance and higher concentrations of free fatty acids, overweight and obese mothers are more likely to 'overnurture' their fetuses [370]. Although the concept of overnutrition does not require an increased birthweight [368], it is well established that maternal obesity is associated with an increased birthweight in the offspring which one could hypothesise could be due to exposure to high glucose and fatty acid concentrations during gestation. Although some of these neonates might be affected by poor placental function and subsequently not live up to their growth potential, some of this might be masked by a higher weight due to overnutrition. These fetuses might not be identified under the current Delphi panel consensus definition of FGR and form a 'masked' group of growth restricted neonates which are not <10th centile but which may display the biometric and functional markers of FGR. No definition for FGR in appropriate-for-gestational age neonates has been established to date.

Placental insufficiency is associated with the majority of FGR cases, although there are various causes of FGR that might lead to placental insufficiency but are not primarily caused by it. These may include maternal etiologies (e.g. cardiac or hypertensive disease, low socio-economic status, maternal age and race) and fetal etiologies (e.g. congenital malformations, infections and genetic abnormalities) [371]. Maternal obesity is associated with a large number of these factors, such as an increased rate of congenital malformations [372], a high rate of preexisting medical conditions [373, 374] and an higher risk of hypertensive disorders in pregnancy [132]. Eventually, no matter the cause, FGR is usually the consequence of inadequate substrates for fetal metabolism and growth, and decreased oxygen availability. [375].

The lack of association could also depend on the restriction of the current study to late FGR, as only neonates born after 37 weeks gestation were included to assure that ultrasonic data at 36 wkGA was available. Diagnosis of early FGR (<32 weeks) relies on the availability of ultrasound data around that gestational age, and the POP study only had data available at 28 or 36 wkGA. Early FGR is associated with impaired placentation, severe fetal hypoxia and high rates of perinatal morbidity [119, 376], whereas late FGR is thought to be milder with lower morbidity and mortality rates [377]. It could be hypothesised that the background of poor placentation and increased inflammation in obesity would be associated with an earlier FGR phenotype than investigated in the current study.

Unexpectedly, when SGA neonates were defined by customised birthweight centiles rather than population-based standards, we found an attenuation for both SGA in the presence and SGA in the absence of FGR markers. As customisation includes adjustment for maternal prepregnancy weight, there is a risk of a circular argument. Furthermore, it was expected that the association between maternal obesity and SGA in the absence of FGR markers would attenuate on customisation, while the association between SGA in the presence of FGR markers was thought to persist when customised birthweight cut-offs were utilised. This finding adds to the debate of the appropriateness of customisation [378, 103], as it suggests that maternal weight may be associated with pathological growth impairment.

Detection of FGR in utero remains challenging, even with the Delphi panel consensus on ultrasonic markers of FGR. Functional MRI could be an other option in studying FGR, as MRI studies are well suited to the analysis of the placental vascular function and physiology, such as blood flow and oxygenation [379] whereas ultrasound measurements only provide an indirect estimated of placental function. Blood flow, perfusion and oxygenation determined by MRI could serve as biomarkers for detrimental changes at every stage of pregnancy, however, to date there is no MRI-based definition of pathological placental function. Additionally, most evidence on functional MRI of the placenta is derived from animal studies, although Chen and colleagues found that FGR was associated with peripheral hypovascularity and hypercellularity in an Intravoxel Incoherent Motion MRI study in term human fetuses [380]. This type of imaging might also be suitable to distinguish 'overnurtured' growth restricted fetuses in obese women based on placental function, without solely relying on birthweight as a criterion for FGR. The clinical value and feasibility of functional MRI studies and consensus on definition of normal placental function will need further investigation, but could aid research into the condition.

The findings in this study have several implications for clinical practice. Although obese women are at risk of poorer perinatal outcomes, enhanced surveillance for diagnosis of FGR is unnecessary in this demographic. It could be hypothesised that poorer outcomes in obese women could be due to a higher rate of congenital abnormalities [372], a higher risk of perinatal complications, such as preeclampsia [132] and gestational diabetes [381], or a higher proportion of pre-existing medical conditions [373, 374]. Consequently, this group of women would benefit from enhanced prenatal screening for comorbidities and increased surveillance for these perinatal complications to improve outcomes.

6.5.4 Conclusion

The rise in obesity worldwide has increased the importance of understanding the outcomes of obese pregnancies. As FGR is linked with many adverse short- and long-term outcomes, identifying neonates at risk can be greatly beneficial. Here we show that maternal prepregnancy BMI was similarly associated with a lower risk of delivering an SGA neonate in the presence or absence of ultrasonic FGR, and obese women were not at higher risk of delivering a pathologically small neonate.

Chapter 7

Discussion

7.1 Chapter summary

Maternal obesity is an increasing problem, with up to 25% of women in the UK entering pregnancy while obese. Pre-, peri- and postnatal weight is not only associated with adverse perinatal outcomes in the current and possible subsequent pregnancies, but also impact on long-term maternal and offspring health. Understanding the associations between maternal obesity, perinatal complications and possible underlying mechanisms is therefore crucial.

There are several key findings from this thesis. Firstly, maternal obesity was associated with impaired cardiovascular adaptation to pregnancy, as shown by a diminished drop in uterine artery vascular resistance. Although fetal growth restriction is thought to originate from poor adaptation to pregnancy, this thesis found a negative association between maternal obesity and the risk of fetal growth restriction. Secondly, gestational weight gain was differentially associated with the risk of developing preeclampsia or fetal growth restriction, adding to the growing body of evidence for divergent mechanisms of these two conditions, despite a common association with underlying placental dysfunction. Lastly, a meta-analysis of published literature found a higher risk of perinatal complications after interpregnancy weight gain while interpregnancy weight loss did not reduce the risk of complications in a subsequent pregnancy. Interestingly, the relative risk of complications was higher in women who started the index pregnancy with a normal BMI, compared to women who were considered overweight or obese at the start of the index pregnancy.

These findings highlight the importance of pre-, peri- and postnatal weight management in women of all BMI categories, in trying to reduce the burden of adverse perinatal outcomes and improve offspring long-term health. This final chapter summarises the main findings of this thesis, discusses the strengths and limitations and highlights the public health relevance of the main findings.

7.2 Framework and approaches

The framework for evaluating the relationship between maternal weight dynamics and both poor adaptation to pregnancy and related perinatal outcomes is shown in Figure 7.1.

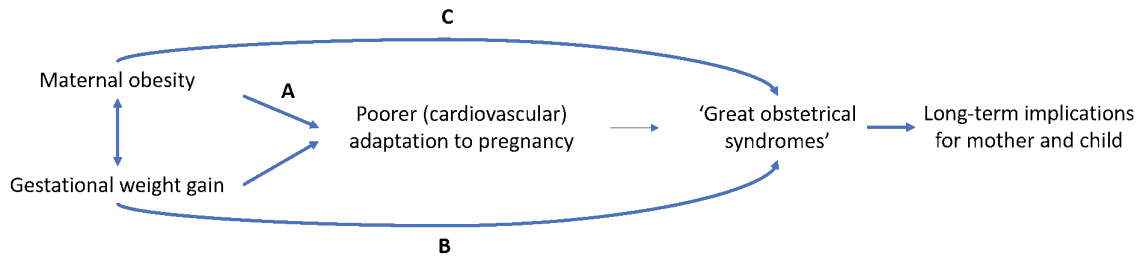


Fig. 7.1 Preliminary framework for evaluating the relationship between maternal pre- and perinatal weight, cardiovascular adaptation to pregnancy and the risk of preeclampsia or delivering a growth restricted neonate.

Four approaches were utilised in this thesis: (i) summarising the relationship between inter-pregnancy weight change and the risk of developing perinatal complications in a subsequent pregnancy (Chapter 2, not shown in the framework), (ii) evaluation of the relationship between obesity and physiological parameters of cardiovascular adaptation (**Chapter 4**, relationship A in the framework), (iii) investigation of the association and the effect of the timing of gestational weight gain (GWG) and the risk of developing preeclampsia or delivering a small for gestational age neonate (SGA) (**Chapter 5**, relationship B in the framework) and (iv) assessment of the association between maternal prepregnancy weight and the risk of fetal growth restriction (**Chapter 6**, relationship C in the framework).

7.3 Summary of main findings

7.3.1 Risk of perinatal complications after interpregnancy weight change

Chapter 2 reported a meta-analysis of seven studies, including a total of 280,672 women. Interpregnancy weight gain of >3 BMI units was associated with a higher risk of developing gestational diabetes (adjusted odds ratio (aOR) 2.37 [95% confidence interval 1.50-3.34]), developing preeclampsia or pregnancy induced hypertension (aOR 1.70 [1.50-1.91] and aOR 1.71 [1.51-1.91], respectively) and delivering a large for gestational age neonate (aOR 1.63 [1.30-1.97]). In contrast, interpregnancy weight loss was associated with a lower risk of

delivering a large for gestational age neonate (aOR 0.79 [0.58-0.99] for loss >1 BMI unit).

Since the publication of the meta-analysis in **Chapter 2**, two further meta-analyses have been published. The first analysis specifically focuses on hypertensive disorders in pregnancy [382], the second analysis reported on similar perinatal outcomes as the analysis in this thesis, but additionally summarised the relationship between interpregnancy weight change and the risk of Caesarean section in a subsequent pregnancy [383].

The study by Martinez-Hortelano and colleagues [382], reporting on hypertensive disorders in pregnancy, stated a similar direction of association between interpregnancy weight gain and the risk of preeclampsia (odds ratio (OR) 1.39 [95% confidence interval (CI) 1.18-1.60]) as the study in this thesis. However, Martinez-Hortelano and colleagues utilised a heterogeneous reference group and additionally pooled crude and adjusted odds ratios together. Furthermore, a study by Mostello and colleagues [233] reporting a slightly lower OR (1.29 [1.20-1.38]) was incorporated in their analysis but excluded from the meta-analysis in this thesis due to overlapping study populations. This could explain why the association reported in their publication is slightly lower than the one observed in this thesis.

The study by Timmermans and colleagues [383] also employed a different reference group to the analysis in this thesis, alternating between a reference group of interpregnancy weight change between -1 and +1 BMI unit and -2 and +2 BMI units. This resulted in an OR for preeclampsia of 1.77 [1.53-2.04] for ≥ 3 kg/m² interpregnancy weight gain. Furthermore, this definition of the reference groups made it possible for them to statistically summarise the effects of interpregnancy weight change on the risk of delivering a small for gestational age neonate and delivering preterm. In their study, BMI loss >1 kg/m² was associated with a lower risk of delivering a small for gestational age neonate (OR 1.58 [1.26-1.98]), although weight loss >2 BMI units was not associated with SGA risk. Similarly, weight loss >1 BMI unit was associated with a higher risk of preterm birth (OR 1.40 [1.08-1.83]) while weight loss >2 BMI units was not associated with a higher risk of delivering preterm. Due to the homogenous reference group defined in the meta-analysis in this thesis, we were only able to summarise the crude risk of delivering an SGA neonate or delivering preterm for the group. We employed a reference group of interpregnancy weight change between -1 and +1 BMI unit, defined the risk of delivering an SGA neonate or delivering preterm for women gaining >1 BMI unit and found very similar associations (crude odds ratio (cOR) 1.53 [1.35-1.71] and cOR 1.45 [1.21-1.69], respectively).

Differences in included time ranges could have contributed to the heterogeneity of results between the meta-analysis in this thesis, and those published by Martínez-Hortelano et al. and Timmermans et al.. While the study in this thesis included women from as early as 1986 [184], the above-mentioned meta-analyses [382, 383] included women recruited as far back as 1959. As described in **Chapter 1**, the incidence of maternal obesity has increased significantly in the past decades and more recent studies could have included a higher proportion of overweight and obese women. Subgroup analyses by maternal BMI category at the start of the first pregnancy, as well as defining weight loss or gain as a percentage change rather than as absolute value could further elucidate this association.

Chapter 1 described the U-shaped trajectory of postpartum weight retention; most women lose (part of) the weight gained over gestation in the 3-12 months postpartum [176]. However, in the longer term (>12 months), excessive GWG was associated with increased postpartum weight retention [177]. A short (>18 months) or long (>60 months) interpregnancy interval is known to be associated with a higher risk of perinatal complications too [384]. It is unclear what the role weight change plays in this association. It could be hypothesised that part of this association is due to a shorter interpregnancy interval being associated with insufficient time to lose the weight gained during gestation, and an increased risk of weight retention in the long term. This association needs further clarification.

7.3.2 Association between maternal weight dynamics and both cardiovascular adaptation to pregnancy and perinatal outcomes

7.3.2.1 Maternal obesity and fetal growth restriction

The results reported in **Chapter 4** showed that maternal cardiovascular adaptation to pregnancy was impaired in obese women compared to normal weight women, as demonstrated by a diminished drop in vascular resistance in the uterine circulation. Although fetal growth restriction is thought to have a background in poor placentation and impaired cardiovascular adaptation to pregnancy, the results reported in **Chapter 6** did not show a higher risk of fetal growth restriction in obese women.

Both maternal obesity (**Chapter 6**) and gestational weight gain (**Chapter 5**) were negatively associated with the risk of delivering a small for gestational age neonate. Before the start of the study, we hypothesised that maternal obesity would be associated with a higher risk of delivering a growth restricted small neonate rather than a constitutionally small neonate, through poor placentation and impaired adaptation to pregnancy. However, maternal

obesity was equally associated with a lower risk of delivering a constitutionally small or pathologically small neonate. One of the arguments explaining the negative relationship between maternal obesity and small for gestational age neonates could be that obese women would expose their fetus to ‘overnutrition’, which could increase overall birth weight and the incidence of delivering a large-for-gestational age neonate as observed in many previous studies. It is possible that the effect of obesity on FGR is not completely captured by assessing growth potential through SGA neonates. A combination of poor adaptation to pregnancy and overnutrition in obese pregnancies could impair a fetus’ growth potential, but not lead to birth weight falling below the cut off for defining an SGA neonate (10th centile). It could be hypothesised that there is ‘unidentified’ growth restriction in non-SGA neonates born to obese mothers. However, there is currently no consensus for the definition of (mild) growth restriction in neonates born slightly above the 10 centile and therefore no suitable way to study this relationship.

7.3.2.2 Gestational weight gain and fetal growth restriction

The negative association between gestational weight gain and the risk of delivering an SGA neonate shown in **Chapter 5**, might highlight a similar ‘overnutrition of the fetus’ hypothesis. Firstly, weight gain during first and second trimester of pregnancy is associated with an increase in adipose tissue in the mother, whereas weight gain during the third trimester seems most likely due to growth of the fetus. The results showed that the association between weight gain and SGA neonates became less strong over the course of gestation, which is consistent with the idea that (early) excess adipose tissue could lead to overnutrition in the fetus and subsequently leads to a higher birth weight. Secondly, as placentation and the first stages of cardiovascular adaptation to pregnancy occur in the first trimester, GWG might not be able to influence these processes. Sensitivity analyses in **Chapter 4** showed no influence of GWG on the relationship between maternal prepregnancy obesity and cardiovascular adaptation to pregnancy. However, we could only assess the impact of GWG from 12 weeks gestation onwards. This could suggest that prepregnancy obesity is more important for impaired cardiovascular adaptation to pregnancy than weight changes during gestation. However, to my knowledge, no studies directly investigating the association between GWG and (physiological parameters of) cardiovascular adaptation to pregnancy have been conducted.

The analyses in **Chapter 5** did not distinguish between constitutionally small and pathologically small neonates when assessing the relationship between GWG and SGA neonates. Previous studies have established a negative relationship between GWG and birthweight (see **Chapter 1**), but no study to date has reported the association between GWG and ultrasonic

markers of fetal growth restriction as proposed by the Delphi panel [101]. However, it would be of great interest to establish whether the negative associations are equal for the risk of delivering a constitutionally small and pathologically small neonates, as interventions to reduce the risk of growth restricted neonates through increased weight gain could then be explored.

7.3.2.3 Gestational weight gain and preeclampsia

Maternal prepregnancy obesity has previously been identified as one of the main risk factors for the development of preeclampsia [130]. Obesity and preeclampsia are thought to share pathways that link the two conditions, such as a low-grade inflammatory state and endothelial dysfunction (see **Chapter 1**). However, the influence of GWG on the development of preeclampsia is less clear. The observed association in **Chapter 5**, between late (28-36 weeks gestational age) weight gain and preeclampsia might not be causal, as preeclamptic women are known to develop oedema, which could in turn lead to weight gain. Furthermore, as hypothesised above, GWG might not influence the underlying mechanisms of preeclampsia (i.e. impaired spiral artery remodelling, endothelial dysfunction, and oxidative stress) as spiral artery remodelling is initiated shortly after implantation and might be completed before any significant weight gain could occur.

7.3.2.4 Divergent associations between preeclampsia and fetal growth restriction

Although both preeclampsia and fetal growth restriction (FGR) are thought to have underlying placental dysfunction, it is unclear why abnormal placentation in some cases leads to FGR and in other cases to preeclampsia. This thesis and other published studies provide several different leads for divergent mechanisms. Firstly, a recent study by Gong and colleagues based on the same POP study showed a divergent metabolic pathway leading to either preeclampsia or FGR. N1,N12-diacetylspermine, a maternal serum polyamine, was positively associated with preeclampsia but negatively associated with FGR [282]. Secondly, the analyses in this thesis highlighted a further two divergent associations between preeclampsia and FGR: (i) the relationship between maternal obesity and preeclampsia is well established, but **Chapter 6** showed a negative association between maternal weight and the risk of FGR and (ii) **Chapter 5** revealed associations in opposite directions between GWG and these great obstetrical syndromes. Lastly, a recent study by Tay and colleagues [365] investigated the relationship between maternal cardiovascular adaptation to pregnancy and both preeclampsia and FGR. They found that the mean uterine artery pulsatility index (corrected for gestational age) was higher in pregnancies affected by FGR or simultaneously affected by FGR and preeclampsia,

but not in pregnancies affected by preeclampsia alone. Although this study did not utilise the definition of FGR defined by the Delphi panel, they did incorporate ultrasonic markers of FGR into the definition. The results of the Tay et al. study only reflect maternal vascular resistance at one timepoint in gestation, but this result warrants further investigation into the relationship between the physiological drop in the uterine artery pulsatility index and both preeclampsia and FGR to shed further light on the divergent pathways leading to these conditions.

As an alternative hypothesis to placental dysfunction being the main cause of FGR, one could hypothesise that a poor state of the peripheral circulation might contribute to poor fetal growth. As discussed in **Chapter 1** and **Chapter 4**, remodelling of the uterine artery circulation is one of the key determinants of adequate utero-placental perfusion, through e.g. flow-mediated or endothelial-induced vasodilation [147, 322]. As both mechanisms seem to be impaired in obese women, this could suggest poor peripheral adaptation to pregnancy in obesity. Additionally, obese women described in **Chapter 4** had higher UtA-PI values at 20wkGA compared to normal weight women, suggesting less adequate spiral artery remodelling in obese pregnancies [318, 316]. When spiral arteries retain some of their smooth muscle layer, vasoconstriction can still occur and lead to ischaemia-reperfusion injury in the placental with subsequent oxidative stress. This might cause further damage to the placental development. Together, this suggests that the poor cardiovascular state in obese women might lead to poor adaptation and subsequently lead to compromised fetal growth.

7.3.2.5 Alternative framework

To summarise the findings in this thesis, in combination with known associations from the literature, the framework proposed in Figure 7.1 must be divided further. Firstly, the relationship between maternal obesity and both preeclampsia and FGR is proposed as in Figure 7.2.

This thesis has shown the positive relationship between maternal obesity and impaired maternal cardiovascular adaptation to pregnancy (**Chapter 4**). Whether this poor adaptation leads to a higher risk of preeclampsia or fetal growth restriction has not been explored in this thesis, but this has been previously established in the literature. Furthermore, in **Chapter 6**, we showed a negative association between maternal prepregnancy BMI and the risk of fetal growth restriction. From this, we can hypothesise that either (i) maternal obesity does not affect the adaptation to pregnancy sufficiently to induce growth restriction, or (ii) growth restriction emerges from different underlying mechanisms.

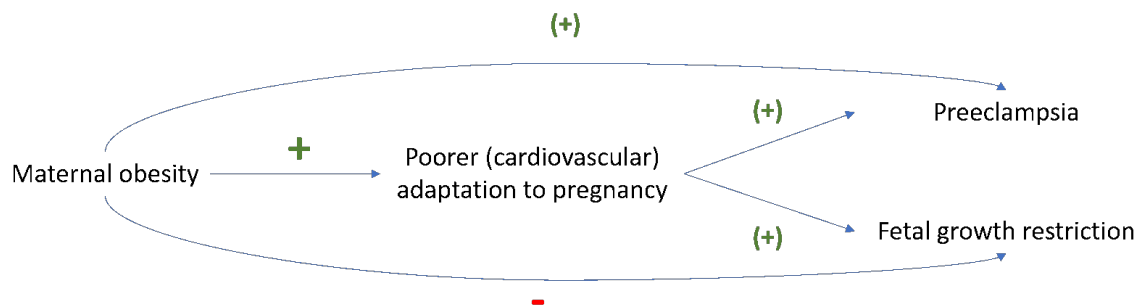


Fig. 7.2 Developed framework of the relationship between maternal obesity, cardiovascular adaptation to pregnancy and the risk of preeclampsia or delivering a growth restricted neonate. Relationships indicated with a + are found to be positive associations in this thesis, relationships indicated with a - are found to be negative, and relationships indicated with a (+) are known positive associations from the literature.

Secondly, the relationships between GWG and both preeclampsia and FGR are summarised in Figure 7.3.

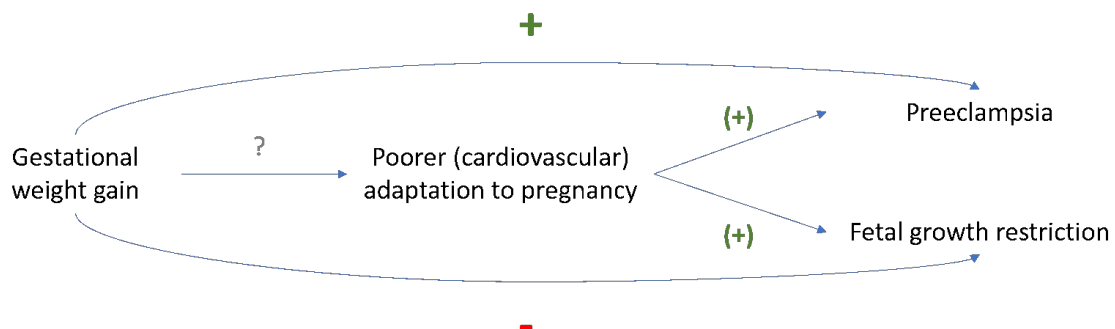


Fig. 7.3 Developed framework of the relationship between gestational weight gain, cardiovascular adaptation to pregnancy and the risk of preeclampsia or delivering a growth restricted neonate. Relationships indicated with a + are found to be positive associations in this thesis, relationships indicated with a - are found to be negative, relationships indicated with a (+) are known positive associations from the literature and relationships indicated with a '?' are currently unknown.

This thesis did establish a positive association between GWG and preeclampsia, yet a negative association between GWG and FGR (**Chapter 5**). As discussed above, these associations are observational and will need to be further explored to confirm or refute causality. Additionally, it would be of great interest to establish whether GWG is associated

with poorer adaptation to pregnancy, as if there is a causal association intervention through adequate weight management can be considered.

7.4 Strengths & Limitations

Specific strengths and limitations have been discussed within each chapter, however there are some factors that are applicable to most analyses in this thesis.

7.4.1 Strengths

A major strength of the POP study is the blinded nature of the ultrasound scans. As both clinicians and patients were blinded to the results of the research scans (at 28- and 36 wkGA) and the research elements of the 20 week scan, the study itself did not interfere with perinatal outcomes. This facilitated the assessment of screening methods for perinatal outcomes, and we could observe physiological patterns of adaptation to pregnancy across the full spectrum without the observations themselves becoming reason for intervention.

Another strength was that the POP study was limited to nulliparous women, as they are known to have a higher incidence of perinatal complications including preeclampsia. The current analyses therefore had enough power to identify associations (it should be noted that power calculations were carried out in the setup for the POP study and were not part of this thesis [266]). Furthermore, one of the strongest predictors of a pregnancy outcome is whether a woman has experienced this outcome in a previous pregnancy. Assessing only nulliparous women makes sure that any observed association is not confounded by a previous adverse complication and therefore requires less adjustment.

The predefined analyses plans in **Appendix C and D** are a further strength of this thesis. In general, but specifically in observational studies, it is wise to develop an analysis plan before exploring the data. The interpretation of observational studies is at risk of bias (e.g. confounding, selection bias) and uncertainty of the role of any unmeasured variables [385]. An previously defined analysis plan, defining the variables of interest, subgroup and sensitivity analyses and statistical methods for analysis, can help reduced the impact of bias on the interpretation. If done correctly and prospectively, observational studies are shown not to overestimate (treatment) effects compared to e.g. randomised trials [386].

7.4.2 Limitations

Although the POP study comprising only nulliparous women was a strength, the exclusion of multiparous women reduces the generalisability of the findings to the overall population. Furthermore, the women in the POP dataset were predominantly white and from a relatively affluent area around Cambridge. As described in **Chapter 1**, there are differences in incidence of preeclampsia and FGR between ethnicity (i.e. the risk of preeclampsia is higher in black women compared to white women), and it could be hypothesised that disparities in adaptation to pregnancy, for example, could underlie these observations. It would therefore be of great interest to explore heterogeneous populations, or to repeat these analyses in a cohort of predominantly non-white women. Similarly, incidences of obesity and patterns of weight gain can differ between different demographics, and this is an area that needs to be further explored as well. Despite the limited diversity in the POP study, other findings that have arisen from this cohort have been successfully replicated in an ethnically diverse and less affluent population from Bradford [279, 79]

Unfortunately, longitudinal data on maternal blood pressure was not available, as only a single value at 12 weeks gestation was recorded for all women. It is known that maternal prepregnancy BMI can influence blood pressure and blood pressure changes throughout gestation [314], which can also influence maternal cardiovascular adaptation to pregnancy. Ideally, this relationship would have been explored in this thesis.

We were unable to properly distinguish between early and late preeclampsia in our analysis, due to unavailability of the time of diagnosis. As described in **Chapter 1**, early and late preeclampsia are thought to have different background mechanisms [52], and therefore it would have been of great interest to study these subtypes separately. Gestational age at birth was available and has been used as a proxy for early and late preeclampsia in this thesis (**Chapter 5**) and in earlier POP study publications [267, 279].

Similarly, we could not discriminate between early and late growth restriction. The Delphi panel established different definitions for early (<32 weeks gestation) or late (>32 weeks gestation) FGR, but as the POP study only conducted research scans at 28- and 36-weeks' gestation, it was impossible to distinguish, as the time cut off for diagnosis is between these scans.

As with all observational studies, there is a risk that uncontrolled or residual confounding influences the results. Although analyses in this thesis were adjusted for seemingly clini-

cally relevant variables, self-reported variables (such as ethnicity) may have had an impact. Furthermore, maternal weight at the booking scan was used as a proxy for prepregnancy weight. Although women are advised to only gain up to 2 kg in the first trimester, according to the IOM guidelines, if there was substantial weight gain during the first trimester, maternal weight and therefore BMI could have been overestimated.

A person's BMI is widely adapted as it is a simple and cost-effective way of tracking obesity at a population level and has formed the backbone of obesity classification and surveillance. However, BMI does have several limitations [387]. Firstly, obesity is defined as excess accumulation of body fat, and it is the excess in fat mass that is the cause of the comorbidities rather than the excess weight. However, BMI is only a surrogate measure for body fat mass. From this, one can argue that the actual body fat percentage should be assessed to develop population standards against which individuals can be compared. Secondly, in some cases, BMI provide misleading information on body fat content. This includes a progressive increase in body fat to lean body mass ratio with aging and a differential relationship between BMI and body fat for different ethnicities. Due to the limitations of BMI, it could be argued that the categorisation of BMI into classifications is unsatisfactory. As large epidemiological studies on body fat content are sparse and no normative standards are developed for comparison of individuals fat mass, BMI is currently the best surrogate measure.

The use of BMI as a measurement of health in pregnancy can also be disputed for the same reasons as mentioned above. Additionally, it has proven challenging to assess body composition throughout pregnancy and separate the various components of GWG [35]. However, mean maternal weight and mean body composition values remain unchanged in the first trimester of pregnancy [388], justifying the use of maternal BMI measured at booking scan as a surrogate measure for prepregnancy BMI. Furthermore, in non-obese women, the correlation between BMI and body fat remains significant throughout pregnancy, although it presents with large confidence intervals [389]. Several equations are available for estimating fat and lean mass throughout pregnancy, however these are rarely corrected for gestational age. Recently, a study by Nassr and colleagues has shown that 'Body Fat Index' (pre-peritoneal fat x (subcutaneous fat divided by height)) was a better predictor of the development of gestational diabetes than BMI [390], but this involved ultrasonic assessment of peritoneal fat and therefore implementation on large scale would be challenging.

7.5 Public Health relevance

7.5.1 Interventions to prevent or reduce maternal obesity

Obesity is a worldwide problem and predicted to worsen over the next decades [391, 392]. It is estimated that >30% of the population in England will have a BMI $\geq 30\text{kg/m}^2$ in the year 2025 [393], and women of reproductive age will undoubtedly be affected too. Maternal obesity is not only associated with perinatal complications, but also with long-term offspring health and increased cardiovascular risk in the mother [202, 205]. If we assume causation and as prepregnancy weight is modifiable, programs and interventions preventing women from being overweight or obese at conception could not only have short term health gains but improve long-term population health.

In their 2016 review, Hanson and colleagues make a case for a public health approach to the obesity crisis [394], as the focus on obesity prevention in women of reproductive age is consistent with the need to address the obesity crisis in the general population. They argue that persistent obesogenic environments make it very hard for individuals to mount effective contra-behaviours and to avoid excess weight gain. A population-based approach to obesity prevention will be needed, to not solely focus in individuals willpower and capability to lose weight, but to stimulate general health [395].

A Cochrane review focussing on effective prepregnancy interventions to promote weight loss in overweight and obese women failed to identify any randomised trials on this topic [396]. Furthermore, a 2014 study investigating how women in London (UK) prepare for pregnancy found that, despite a high level of planned pregnancies, very few women were aware of their preconception health [396]. Amongst healthcare professionals it is unclear where the responsibility for preconception care lies. Most healthcare professionals pointed towards primary care, although general practitioners felt that they are seldom involved in preconception care [397]. Together, this highlight a critical need for high quality evidence to support preconception care.

7.5.2 Identification of increased perinatal complication risk in normal weight women after interpregnancy weight gain

As analyses in **Chapter 2** revealed, normal weight women who gain weight between pregnancies are at a relatively higher risk of adverse perinatal outcomes after small increments of weight gain than women who started the index pregnancy overweight or obese and gain

small amounts of weight. This finding is somewhat surprising as normal weight women are usually not identified as being at risk. The National Institute for Health and Care Excellence (NICE) guidelines in the UK only recommend discussing weight with overweight or obese women at their 6-8 weeks postpartum check-up and does not mention postpartum weight management in women who entered pregnancy with a healthy BMI. Making normal weight women aware of the risk of perinatal complications after small amounts of weight gain, could impact outcomes in a subsequent pregnancy.

Although awareness about preconception health among women is low, many women are motivated to adopt healthier lifestyles around pregnancy [398]. This is illustrated by reduced smoking rates in women trying to conceive [396], as well as the resolution of women to seek weight loss information in the postpartum period [187]. However, little is known how this perception and motivation differs between women of different BMI categories. It would be of great interest to investigate awareness amongst normal weight women and healthcare professionals on the perception of risk for adverse perinatal outcomes in a subsequent pregnancy, to be able to provide preconception and postpartum weight guidance in these women.

The analyses in **Chapter 2** did identify the risks associated with interpregnancy weight gain but failed to show a positive association of interpregnancy weight loss on perinatal outcomes. Recommendations for interpregnancy weight management could therefore mainly focus on weight maintenance as opposed to weight loss. As discussed in **Chapter 1**, postpartum weight management seems to be most effective when combination of individual dietary advice and physical activity under professional supervision was offered [191]. For both preconception as well as postpartum interventions the optimal timing is unclear. Lastly, although perinatal outcomes are important to consider, the effects of weight management on cardiovascular adaptation to pregnancy are also key and will contribute to our understanding of the pathophysiology of short-term and long-term maternal outcomes. These should be taken into account in future studies addressing preconception and postpartum health.

7.5.3 Healthcare costs associated with maternal obesity and perinatal outcomes

Lastly, in addition to the health of the mother and neonate, the costs to the healthcare system relating to the management of adverse outcomes should also be considered. For instance, preeclampsia is associated with a mean incremental cost of \$28,603 (~£23,000) per mother–infant pair compared to uncomplicated pregnancies, as identified by an American

study [399]. As 15% of all early preeclampsia cases are estimated to be attributable to maternal prepregnancy weight, a reduction in the incidence of maternal obesity can not only improve health outcomes, but also lighten the financial burden on healthcare systems [133].

An individual participant meta-analysis by the National Institute for Health Research aimed to investigate the cost-effectiveness of diet- and exercise-based interventions in pregnancy [400]. Their model predicted that perinatal care for women in the intervention arm would cost £147 more than care for women without intervention. Although the intervention prevented cases of preeclampsia, gestational diabetes and pregnancy induced hypertension, the cost of avoiding one case of preeclampsia was £306,000, which is significantly higher than the willingness to pay threshold in the UK [401]. A secondary analysis of the cost-effectiveness of perinatal diet- and exercise-interventions in women of different BMI categories revealed that, although the cost of avoiding one major perinatal complication was lowest in obese women, not one subgroup reached the willingness to pay threshold. Further development of evidence-based interventions to prevent excessive GWG or reduce postpartum weight retention should take the cost of interventions into account to aid nationwide implementation.

7.6 Conclusions

Maternal obesity is associated with impaired cardiovascular adaptation to pregnancy, although prepregnancy weight is not associated with a higher risk of FGR. Gestational weight gain is associated with a lower risk of delivering an SGA neonate and a higher risk of developing preeclampsia, and the timing of the weight gain has a significant impact on these associations.

As maternal obesity is also differentially associated with preeclampsia and the risk of FGR, it could be hypothesised that the pathophysiology of these syndromes differs, despite shared backgrounds in placental dysfunction. Further research into the divergent pathways of these two conditions is needed. If causality is assumed, interventions that are aimed at reducing the SGA incidence without increasing the risk of preeclampsia are optimally targeted in the second trimester of pregnancy.

To conclude, weight management pre-, peri- and postnatally is of great importance in reducing the burden of adverse pregnancy outcomes and optimising the long-term health in the mother and the offspring. Further research is needed to identify the optimal methods and periods of interventions to reduce weight gain and obesity in women of reproductive age.

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Appendix A

List of publications authored during PhD

These are publications from work directly related to the PhD and other projects carried out before starting my PhD (marked with *).

Published

Teulings NEWD, Wood AM, Sovio U, Ozanne SE, Smith GC, Aiken CE. Independent influences of maternal obesity and fetal sex on maternal cardiovascular adaptation to pregnancy: a prospective cohort study. *International Journal of Obesity*. 2020 Jun 15:1-0.

***Teulings NEWD**, Garrud TA, Niu Y, Skeffington KL, Beck C, Itani N, Conlon FG, Botting KJ, Nicholas LM, Ashmore TJ, Blackmore HL. Isolating adverse effects of glucocorticoids on the embryonic cardiovascular system. *The FASEB Journal*. 2020 Jun 5.

Teulings NEWD, Masconi KL, Ozanne SE, Aiken CE, Wood AM. Effect of interpregnancy weight change on perinatal outcomes: systematic review and meta-analysis. *BMC pregnancy and childbirth*. 2019 Dec 1;19(1):386.

Submitted

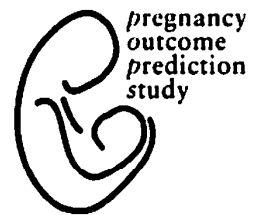
Teulings NEWD, Sovio U, Smith GC, Wood AM. Timing of gestational weight gain and the risk of developing preeclampsia or delivering a small-for-gestational age neonate; a prospective cohort study. (*submitted to BJOG*)

In preparation

Teulings NEWD, Sovio U, Wood AM, Smith GC. Relationship between maternal prepregnancy body mass index and ultrasonic markers of fetal growth restriction in small for gestational age fetus; a prospective cohort study.

Appendix B

**Self-reporting questionnaire for
maternal demographics in the Pregnancy
Outcome Prediction Study at 20 weeks
gestational age**

DEMOGRAPHICS

Addressograph Label

Current age

Marital status

Married

Cohabiting

Single

Occupation

Partners Occupation

What age did you complete full time education.

Smoking status

Never Quit (before preg) Quit (during preg)
Currently smoking per day

Alcohol (units per week)currently

Current prescription medication

Current medical conditions

Previous miscarriages of less than 20 weeks Y / N Date weeks

Were you using the contraceptive pill in the three months before your pregnancy

Yes

No

Date of last menstrual period

Certain Yes No

Duration of menstrual cycle (eg 28 days)

Menarche/OCP questions**1 Age periods started**

Please circle any methods of contraception you have used and for how long

- a. Combined Pill years
- b. Mini pill years
- c. Hormonal inter-uterine device years
- d. Norplant or Depo-Provera (injection) years
- e. Other methods (e.g. condoms) years

How many years have you used contraception in total

How long has it taken you to become pregnant from stopping contraception?

Appendix C

Predefined analysis plan to investigate the association and timing of gestational weight gain on adverse perinatal outcomes in the Pregnancy Outcome Prediction Study cohort

C.1 Aim

To investigate the association and timing of gestational weight gain on adverse perinatal outcomes in the Pregnancy Outcome Prediction Study cohort

C.2 Exposure

C.2.1 Primary exposure

Primary exposure will be the rate of gestational weight gain. Maternal weight was measured by research midwives at the first, second, third and fourth scanning appointment, equating to 12-, 20-, 28- and 36-weeks' gestation respectively. We will investigate the weight gain between two consecutive appointments (e.g. between 12 and 20 weeks, between 20 and 28 weeks and between 28 and 36 weeks).

Preconception BMI	Total weight gain		Incremental weight gain during second and third trimester	
	Range (kg)	Range (lbs)	Mean (range) in kg/week	Mean (range) in lbs/week
Underweight (<18.5 kg/m ²)	12.5-18	28-40	0.51 (0.44-0.58)	1 (1-1.3)
Normal weight (18.5 - 24.9 kg/m ²)	11.5-16	25-35	0.42 (0.35-0.50)	1 (0.8-1)
Overweight (25.0 - 29.9 kg/m ²)	7-11.5	15-25	0.28 (0.23-0.33)	0.6 (0.5-0.7)
Obese (≥30 kg/m ²)	5-9	11-20	0.22 (0.17-0.27)	0.5 (0.4-0.6)

Table C.1 Institute of Medicine gestational weight gain recommendations throughout pregnancy [15]

Gestational age (GA) varied around the planned appointments (e.g., the 12-week planned appointment took place between 10-14 weeks GA etc.). Preliminary data analyses have shown that maternal weight varied very little by GA at the 12-week planned appointment, but it did vary by GA later in pregnancy. To address the issue of variable GA around the planned visits, we will estimate the weight gain per 8-week GA interval (ie, 12-20 weeks, 20-28 weeks and 28-36 weeks) for each mother using a mixed effects linear regression model.

C.2.2 Secondary exposure

Secondary exposure will be similar to the primary exposure, but rather than gestational weight gain per GA interval it will be defined as total gestational weight gain (i.e. weight gain between 12- and 36-weeks).

C.2.3 Alternative classification of exposure

Furthermore, we will investigate gestational weight gain classified as inadequate, adequate or excessive, as classified by the National Academy of Medicine [15]. These exposures will be defined 1) between 12 weeks and 36 weeks, and 2) between each set of two consecutive appointments. See C.1 for reference of total weight gain and weight gain rates per trimester. The classifications of ‘inadequate’, ‘adequate’ and ‘excessive’ will be extracted from the model predicting the gestational weight gain rate (see primary exposure) to account for gestational age at appointments.

C.3 Outcomes of interest

C.3.1 Primary outcome

The primary outcomes will be:

- Small-for-gestational age (defined as birthweight <10th centile, using fetal sex and gestational age adjusted reference standard derived from a UK population and described in [341])
- Preeclampsia (defined as per 2013 ACOG classification)

C.3.2 Secondary outcomes (if time permits)

- Uterine artery doppler values measured at 20-, 28- and 36-weeks gestation
- Physiological drop of the uterine artery doppler, defined as the difference in absolute values between the earlier scan and a later scan (e.g. value at 20 weeks minus the value at 36 weeks).
- Abnormal uterine artery dopplers, defined as a uterine artery pulsatility index above 95th centile at the 36-weeks scan using the distribution within the POPS cohort.

C.3.3 Effect modifiers

We will investigate maternal BMI as a possible effect modifier. Maternal BMI will be considered as a continuous variable, as well as being classified as per WHO definitions (underweight as BMI <18.5 kg/m², normal weight as BMI 18.5-24.9 kg/m², overweight as BMI 25-29.9 kg/m² and obese as BMI >30 kg/m²).

C.4 Analytical approach

Summary statistics will be used to describe the characteristics of the women by exposure of interest.

We will use a two-step modelling approach. In step 1 we will estimate the weight gain per GA interval (ie, 12-20 weeks, 20-28 weeks and 28-36 weeks) for each mother using a mixed effects linear regression model. The mixed model will regress weight on the difference in GA between the planned and actual visit (fixed effect), and a random intercept for each mother will be estimated to account for the dependency between repeated measures. The model can be written as:

$$Y_{ij} = a_j + b_j d_{ij} + u_i + e_{ij}$$

where

Y_{ij} is the weight for mother $i=1, \dots, n$ at scan visit $j=1, \dots, 4$

d_{ij} is the difference in GA between the observed GA (t_{ij}) and planned GA (eg, $d_{i1} = t_{i1} - 12$, $d_{i2} = t_{i2} - 20$, $d_{i3} = t_{i3} - 28$, $d_{i4} = t_{i4} - 36$)

a_j denotes the average maternal weight at scan visit $j=1, \dots, 4$ at the planned GA 12, 20, 28 and 26 weeks respectively.

b_j denotes the linear change in weight around scan visit $j=1, \dots, 4$

u_i denotes a mother-specific weight across all scan visits, assume $u_i \sim N(0, \sigma^2)$

e_{ij} denotes the residuals, assume $e_{ij} \sim N(0, \sigma^2)$

A corrected weight (Y_{ij}^*) for the planned scan can be simply estimated as $Y_{ij}^* = Y_{ij} - b_j d_{ij}$. Similarly, estimated weight gains per GA interval can be estimated, e.g. for 12-20 weeks $Y_{i[20-12]}^* = (Y_{i2} - b_2 d_{i2}) - (Y_{i1} - b_1 d_{i1})$.

In step 2, associations between the estimated weight gain per GA interval and primary outcomes of interest will be quantified using hazard ratios from Cox proportional hazard models, using gestational age as the time scale or using odds ratios from the logistic model. We will also explore possible non-linear associations (e.g. using fractional polynomials).

If time permits, the relationship between uterine artery dopplers or physiological drop in uterine artery pulsatility index will be assessed by mixed linear regression models.

Effect modification by maternal BMI category will be assessed by using the χ^2 test for heterogeneity. Confounders that will be considered are maternal age, fetal sex, maternal ethnicity and deprivation index.

For all outcomes, except gestational diabetes and preterm birth, we will investigate the relationship between the rate of gestational weight gain between 12-20 weeks, 20-28 weeks and 28-36 weeks. However, as the diagnosis for gestational diabetes is usually made at around the 28-week timepoint, we will only investigate the relationship between gestational

diabetes and the rate of weight gain between 12-20 weeks and between 20-28 weeks.

For statistical analysis and data presentation we will use R for windows, version 3.4.2 The analysis will be conducted on an anonymised dataset. The anonymised data provided by the POP study will be held in encrypted files and analysed within the Cambridge Biomedical Research Campus. The proposed analyses are covered by ethical approval granted to the POP study (REC Ref: 07/H0308/163).

C.5 Presentation of results

At the end of the analysis, we plan to submit a paper to a peer-reviewed journal in the field of perinatal health. The analysis will be included in a PhD thesis funded by the British Heart Foundation. Any additional costs associated with performing the analysis will be met by the British Heart Foundation studentship awarded to Noor Teulings.

Appendix D

Analysis plan for assessing the relationship between maternal prepregnancy BMI and ultrasonic markers of fetal growth restriction in small-for-gestational age fetus in the Pregnancy Outcome Prediction Study

D.1 Aim

To investigate the relationship between maternal BMI and the presence of ultrasonic markers of fetal growth restriction in fetuses born small-for-gestational age.

D.2 Exposure

D.2.1 Primary exposure

Primary exposure will be maternal BMI (calculated as maternal weight at 12-week research appointment divided by maternal height squared). As the primary exposure, maternal BMI will be considered as a continuous variable.

D.2.2 Secondary exposure

Maternal BMI will be classified as normal weight as BMI $<25.0 \text{ kg/m}^2$, overweight as BMI $25\text{-}29.9 \text{ kg/m}^2$ and obese as BMI $>30 \text{ kg/m}^2$.

D.3 Outcomes of interest

D.3.1 Primary outcome

Primary outcome will be fetus born small-for-gestational age (SGA) in the presence or absence of (ultrasonic markers of) fetal growth restriction (FGR). Small-for-gestational age will be classified as BW $<10^{\text{th}}$ percentile using fetal sex and gestational age adjusted reference standard based on the UK population [341].

FGR will be defined based on birthweight percentile [341] and two components of the Delphi panel consensus [101] as either

- (i) birthweight $<3^{\text{rd}}$ percentile
- (ii) birthweight $<10^{\text{th}}$ percentile PLUS either
 - (a) slow growth velocity, defined as AC AND/OR EFW crossing percentiles > 2 quartiles from 20 weeks gestation to 36 weeks gestation visit or from 28 weeks gestation visit to 36 weeks gestation visit (equivalent to a change in z score of less than -1.35 in the POP study) OR
 - (b) pulsatility index of the umbilical artery above 95th percentile at 36 wkGA using Acharya reference [361]

The reference group will be babies born at a healthy weight (BW $\geq 10^{\text{th}}$ percentile [341]) with or without markers of fetal growth restriction (as classified above).

Women with preterm birth (<37 weeks), will be excluded from this analysis, as most of them did not have a scan at 36-weeks' gestation.

D.3.2 Secondary outcome

We will repeat the above analysis

- (i) using a severe SGA criterium (BW <3rd percentile)
- (ii) using BW <10th percentile + two components of the Delphi panel consensus [101].

D.4 Analytical approach

Summary statistics will be used to describe the characteristics of the women by exposure of interest. Continuous variables will be compared using the Kruskal-Wallis one-way analysis of variance and categorical variables with the chi-square test.

Possible confounders will be explored by assessing the relationships between maternal characteristics and maternal BMI and SGA with and without FGR markers.

Logistic regression analysis will be used to explore the relationship between maternal BMI (continuous and categorical) and (i) the risk of delivering an SGA neonate without markers of FGR during gestation (ii) the risk of delivering an SGA neonate showing any or specific markers of FGR during gestation, with adjustment for potential confounders. To formally assess whether the presence of FGR ultrasonic markers modifies the relationship between maternal BMI and SGA, a further logistic regression analysis will be performed on the SGA outcome, with an interaction term between maternal BMI and the presence of FGR markers.

We will execute some sensitivity analyses:

- Exclude large-for-gestational age neonates from the control group
- Repeat the analysis, but have severe SGA (classified as BW <5th percentile) as the outcome
- Repeat the analysis using customised birthweight centiles based on the Bulk calculator GROW from the Perinatal institute.
- Repeat the analysis but using SGA plus or minus severe perinatal complications as outcome [104].
- Investigate the relationship between maternal BMI and an SGA neonate plus low PIGF levels, classified as the lowest decile within the POPS cohort.

Analysis will be done in RStudio for Windows, version 1.1.423.

D.5 Presentation of results

At the end of the analysis, we plan to submit a paper to a peer-reviewed journal in the field of perinatal health. The analysis will be included in a PhD thesis funded by the British Heart Foundation. Any additional costs associated with performing the analysis will be met by the British Heart Foundation studentship awarded to Noor Teulings